SOME FACTORS AFFECTING ENERGY METABOLISM IN THE NEW BORN

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D. M. Flynn.

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C O N T E N T S

Note on abbreviations used in the thesis.

T_E Environmental temperature.

B.M.R. The Basal Metabolic Rate.

$\dot{V}O_2$ Oxygen consumption.

pO_2 Partial pressure of oxygen in mm. of mercury

pCO_2 Partial pressure of carbon dioxide in mm. of mercury.

in the warm Environmental temperature conditions in which the metabolic rate is minimal.

in the cool Environmental temperature conditions below the critical temperature in which metabolic rate is increased.

Other occasionally used abbreviations are explained in the text.

CHAPTER 1

INTRODUCTION

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INTRODUCTION

"And the Lord God formed man of the dust of the ground, and breathed into his nostrils the breath of life; and man became a living soul." (Genesis 2, 7.)

"And it came to pass that the son of the woman fell sick . . . and there was no breath left in him. And he (Elijah) stretched himself upon the child three times and cried unto the Lord . . . and the soul of the child came into him again and he revived."
(I Kings 17)

Some of us do not believe in Genesis or Kings, and some of us do not believe in God but these are fitting texts and their full implications remained unrealised for generations. It is with the ability of the newborn infant to survive without "the breath of life" that we are concerned.

The fate of infants who have survived postmortem caesarean section provides very good, and perhaps the best evidence of the ability of babies to withstand anoxia. According to Young (1944), in his excellent history of caesarean section, in former times the operation was almost invariably performed only after the death of the mother.

Caesarean section is twice mentioned by Shakespeare. The last desperate hope of Macbeth, based on the words of the apparition:-

". . . for none of woman born
Shall harm Macbeth." (Act IV, Sc. 2)

was destroyed when Macduff declared the manner of his birth

"Tell them Macduff was from his mother's womb
untimely ripped." (Act V, Sc. 7)

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In this context "untimely" can only mean that Macduff was not "born of woman", but from a corpse. As the name implies the same is true of Posthumus in Cymbeline.

"Lucina lent me not her aid
But took me in my throes
That from me was Posthumus rip't".
(Cymbeline Act V, Sc.4)

On the other hand the damaging effects of prematurity, presumably with anoxia are shown by Richard III with his physical deformities:-

"Deformed unfinished, sent before my time
Into this breathing world, scarce half made up
And that so unfashionable
That dogs bark at me as I halt by them."
(Act I, Sc. 1)

And his behaviour disorder,

"A hellhound that doth hunt us all to death ...
This carnal cur."
(Act 4, Sc. 4)

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"Problème d'Harvey" (1651a)

Harvey observed the resistance of the newborn infant to anoxia and posed the question of why it could continue without breathing whether it was in amniotic fluid or in water and how its powers of resistance disappeared after the first breath.

"How is it that if the foetus is expelled with the membranes unbroken it can survive some hours without risk of suffocation, whilst the same foetus, removed from its membranes, if air has once entered the lungs cannot live a moment without it but dies instantly." "In difficult labours it often happens that the foetus is retained in the passages many hours without the possibility of breathing yet is found to be alive. In like manner children have been removed alive from the uterus by caesarean section many hours after the death of the mother. Buried as they are within the membranes they have no need of air but as soon as they have once breathed, although they be returned immediately within the membranes they perish if deprived of it.
. . . it is an established fact that if the foetus has once respired it may be more quickly suffocated than if it had been entirely excluded from air."

"I have often seen the human foetus extracted alive when the mother has been dead some hours. I have also known the rabbit and hare to survive when extracted from the uterus of the dead mother."

Two hundred years later Paul Bert (1870) was to refer to Harvey's observations as the "Problème d'Harvey."

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The work of Boyle (1672).

Perhaps the first scientific investigation of the ability of animals to withstand anoxia was made by Boyle (1672) in the series of experiments with the "exhausted receiver." Two "Titles" in the course of "New pneumatical experiments about respiration" may be mentioned in which Boyle observed the behaviour of animals "accustomed to live for some time without breathing."

Title I was "Observations made about the lasting of ducks included in the exhausted receiver." "Nature having furnished ducks . . . to enable them . . . to forebear for a pretty while respiring under water without prejudice, I thought it worth the trial whether such birds would much better than other animals endure the absence of air in the exhausted receiver." A fully grown duck was reduced to a gasping condition within 2 minutes and it did not appear that "... the duck was able to hold out considerably longer than a hen or other bird non aquatick would have done." In a receiver of similar size containing normal air the duck was in good condition after 5 times as long.

In the course of many similar experiments he made a study "Of the phenomenona afforded by a new kittened kittling in the exhausted receiver." (Title IV) "Being desirous to try whether animals that had lately been accustomed to live either without any or without a full respiration would not be more difficult or slowly killed by the want of air than others which had been longer used to free respiration; we took a kittling that had been kittened the day before and put it into

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a very small receiver." The air was then sucked out. Within one minute or a little more "the little animal had some violent convulsions and lay as dead, but upon letting in of the air he did in a trice show signs of life."

Another kittling was revived with difficulty after 6 minutes in the evacuated receiver. "Wherefore thinking it severe to make him under go the same measure again we sent for another." Air was let in the receiver after a third kittling had been inside for 7 minutes. "Upon which the little creature that seemed stark dead before, made us suspect that he might recover; but though we took him out of the receiver and put aqua vitae in his mouth yet he irrecoverably died in our hands." His conclusion was highly important. "It appears that those animals continued three times longer in the exhausted receiver than other animals of that bigness would probably have done."

Anoxia was not the only factor. Although the pressure in the receiver in these experiments was not stated it was probably near the vapour pressure of water at room temperature (approximately 18 mm Hg., Hodgman, 1955). This may have accounted for the fact that the body and neck of a viper "grew prodigiously tumid and a blister appeared on the back," and for the swelling seen in ducklings, frogs and possibly kittens.

The work of Bert.

Paul Bert (1870) noted that Haller (1761) amongst others, had confirmed Harvey's basic observations although he omitted reference to Boyle. Bert mentioned that the resistance to anoxia did not disappear after the first breath. Berard (1853) had suggested that

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the phenomenon of the resistance to drowning of newborn infants was due to the persistance of foetal channels through the heart i.e. the foramen ovale and the patent ductus but the experiments of Bert were to disprove this theory.

Bert observed that newborn rats displayed the same resistance to anoxia when they were breathing nitrogen, and that the resistance to anoxia persisted in the rat after the foetal channels had been obliterated. This occurs at about the tenth day when resistance to anoxia is still greater than in the adult. He also noted that prolonged gasping in nitrogen continued after the heart had been destroyed. Bert made two other basic observations:-

1). That resistance of newborn kittens to drowning was inversely proportional to the temperature of the water.

2). That the resistance decreased rapidly with age. Newborn rats in nitrogen survived for 50 minutes at ages of 1 day or less but by the age of 17 days the resistance to anoxia had fallen to adult levels and survival was limited to about 3 minutes.

After the work of Bert the focus of interest in the newborn changed to observations on the newborn infant, and we are chiefly concerned with measurements of gaseous metabolism.

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SURVEY OF MEASUREMENTS OF METABOLIC RATE IN NEWBORN INFANTS.

The first recorded measurement of respiratory metabolism appears to be that of Forster (1877) who obtained a value for the carbon dioxide output of a 14 day old infant of 7.89 mls. CO_2 min. Kg. This is rather higher than that found by subsequent workers (e.g. Cross, Tizard and Trythall (1957) found 5.4 ml^s/min. Kg). Other observations were made towards the end of the nineteenth century but it was not until 1904 that satisfactory measurements of oxygen consumption and carbon dioxide appear to have been performed.

The work of Hasselbalch (1904) is interesting because he took particular care to have infants in a very quiet condition. He used naked infants at an environmental temperature of 31-35°C which later authors have found to be the neutral temperature zone. The age of his subjects was one day or less. He found a carbon dioxide production of 4.5-5.0 mls/Kg. min and interestingly there was no correlation between carbon dioxide production and rectal temperature. He also observed the increase in activity in a cold environment which has subsequently been well documented.

The first extensive investigations were those of Benedict and Talbot (1915), and they stated that with the exception of the work of Hasselbalch there were almost no reliable observations on the character of the catabolism of the newborn infant until that time. They studied the oxygen consumption and carbon dioxide production of no less than 94 infants aged less than one week. They observed the fall in respiratory

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quotient in the first 24 hours and subsequently, a finding which has been amply confirmed. The amount of restlessness was recorded on a kymograph and it was found that restlessness could increase the oxygen consumption by at least 65%. They were also able to derive a formula for basal metabolic rate and related it to length and to the square of the cube root of the body weight.

$$C = l \times a \times b \times \sqrt[3]{W^2}$$

where C = Total heat production (Kilocals per 24 hours)

l = length cm.

a = constant = 12.65

b = constant = 10.3

W = Weight, Kg.

Kestner and Knipping (1924) and Kestner (1926) and a number of workers in Germany, obtained standard values for infant metabolism but none of their work was concerned with infants aged less than 1 week. In the 1920's Levine and Wilson (1926) made many observations on infants using an open circuit apparatus but all were concerned with basal values. Murlin, Conklin and Marsh (1925) studied full term infants of less than 1 week old.

Eckstein (1926) concluded from experiments in which infants were placed in water baths at different temperatures that premature infants had no important defect in their response to different environmental temperatures.

Mordhorst (1932) showed that clothed infants increased their oxygen consumption in cool air by 30% but he dealt mainly with premature infants aged more

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than one week. Blackfan and Yaglou (1932) studied the effect of atmospheric conditions on the management of premature infants.

Most of the early work, although not all (see above), on metabolic rate on the normal newborn infant was concerned with establishing values for "basal" metabolic rates and was not concerned with the response of the metabolic rate to environmental temperature. Only in recent years has the effect of environmental temperature been thoroughly investigated. The work of Day is an outstanding exception.

Day (1943) made perhaps the most comprehensive survey of heat balance of premature infants in the literature. Day and his associates used an open circuit apparatus to measure the carbon dioxide output and oxygen consumption, and from this calculated the heat production. Simultaneously the heat losses by evaporation were measured by collecting and weighing the water evaporated, and the heat lost by radiation and convection was measured by converting the respiratory chamber into a direct calorimeter. Thermocouples were placed on the inner and outer surfaces of the copper walls of the chamber and the instrument was calibrated by finding the temperature gradient resulting when known sources of heat were placed inside. By comparison with the calibration results the heat production from an infant was assessed. Heat storage or loss from the infant was calculated from changes of rectal and cutaneous temperature. There was an excellent correlation between calculated heat production and measured heat loss.

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Day found that heat production in cooler air was greater than in warm air. Heat production rose linearly as the air temperature was lowered and inspection of the regression line shows that heat production was about 80% greater at an air temperature of about 27°C than at 33°C. He also pointed out that in (premature) infants the increase in heat production began at higher environmental temperatures than in adults and that their skin temperature was greater. The thermal conductance was not influenced by the level of rectal temperature, which was usually below 98.6°F, and he suggested that "skin seems to have a thermostatic control which is independent to a considerable extent of the inner body temperature but which is responsive to air temperature." Crying and bodily activity were greater in cool air.

In the years following 1940 the work on oxygen consumption in newborn infants and on the resistance of newborn animals to anoxia began to overlap, and then to coincide. Since 1958 work on oxygen consumption in anoxic newborn animals has developed rapidly. Before considering this aspect two further important papers on basal metabolic rate must be described.

Karlberg (1952) made a comprehensive review of the literature until that date and published the result of his own extensive investigations on infants aged 1 week to 1 year. He used a closed circuit apparatus and measured metabolism under basal conditions. He deduced a relationship between energy

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metabolism and weight that could be expressed in a formula:-

$$C = W^b \times k$$

C = Energy metabolism, cals/24 hours

W = Weight, Kg.

where b was a constant equal to the power 0.918, and k a constant equal to 58.6.

In an open circuit Karlberg measured the oxygen consumption in 6 newborn full term infants aged less than 1 week. Karlberg's appendix 5 summarized the literature on measurements of metabolic rate in infants at different ages. The total number of babies aged less than 1 week in whom measurements of basal metabolic rate were published between 1900 and 1950 was about 200, and 94 of these were studied by Benedict and Talbot in 1915. Between 1930 and 1950 measurements of basal metabolic rate were published on only 9 babies aged less than 1 week. From the same table it appears that nothing on the subject was published by British authors between 1843 and 1951.

In 1957 Cross, Tizard and Trythall made the first British contribution to measurements of neonatal gaseous metabolism for many years. Using the body plethysmograph and an open circuit apparatus Cross and his colleagues measured the basal metabolic rate in 47 full term and 21 premature infants most of whom were aged less than 10 days. Simultaneous measurements of the minute volume were made and they were careful to ensure that the infants were asleep. The mean oxygen consumption was 6.99 mls/min/Kg. and

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the mean carbon dioxide production 5.46 mls/min/Kg. There was a significant rise in metabolic rate in the first three days and strong correlation between oxygen consumption and body weight, and oxygen consumption and minute volume. There was also a significant rise in metabolic rate and a significant fall in respiratory quotient in the first few days. Both these results have been confirmed but have not been completely explained. (Confirmed by Hill and Rahimtulla (1965) oxygen consumption, and Brück (1961) respiratory quotient). In the following year Cross and his colleagues published another important paper in which they investigated some factors in the ability of the newborn infant to resist anoxia. The object of our work was to repeat their investigations.

To place their second paper in perspective it is necessary to return to the experimental work on the ability of newborn animals to withstand anoxia and to consider some of the advances in this field after the work of Paul Bert (1870).

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RESISTANCE OF THE NEWBORN TO ANOXIA.

Fazekas, Alexander and Himwich (1941) confirmed the extraordinary capacity of the newborn of various species to resist anoxia. While adult rats exposed to pure nitrogen at environmental temperatures of 24°C succumbed after approximately 3 minutes, one day old rats survived for approximately 50 minutes. In other newborn animals the average survival time was also extremely long but was inversely related to maturity at birth. Newborn cats survived 20 minutes, newborn dogs 23 minutes but rabbits survived only 17 minutes and guinea pigs lived for only 7 minutes in pure nitrogen, all at 24°C. Newborn rats are immature, blind, hairless and helpless but the newborn guinea pig in comparison is relatively mature, and it walks and runs within an hour of being born.

The ability to survive decreased very rapidly after birth and the 17 day old rat survived no longer in nitrogen than did the adult. Dogs mature more slowly than rats and in these animals survival time did not fall to adult levels until the age of about 30 days. The tolerance extended to unborn animals and it was found that foetuses could survive for at least several minutes after the anoxic death of the mother. The tolerance to anoxia was greatly decreased by exposure to higher environmental temperatures.

Since the arterial blood measured in puppies, breathing nitrogen, contained virtually no oxygen after the first few minutes of anoxia, and since the

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animals survived while breathing pure nitrogen Himwich and his colleagues concluded, on the unstated assumption that metabolism must continue during hypoxia, that there must be anaerobic sources of energy. Himwich, Bernstein, Herrlich, Chester and Fazekas (1942) showed that if glycolysis was inhibited by iodoacetate or sodium fluoride the ability to survive anoxia decreased from 50 minutes to values very close to adult levels. The findings of this paper have been considerably extended and amply confirmed. Although Fazekas et al. (1941) found that the in vitro oxygen uptake of slices of brain was very low at birth and increased as the tolerance to asphyxia fell, other evidence shows that the ability to survive asphyxia is related to factors other than the central nervous system (see "Effect of anoxia in a warm environment" page 38).

Mild hypoxia in newborn babies.

It is clear that the effects of complete anoxia cannot be studied experimentally in babies. On the other hand it is justifiable to induce mild ethically acceptable hypoxia in newborn infants. The problems of hypoxia and anoxia are very different, but related and the investigation of the response to hypoxia has shed much light on the ability of the newborn baby to withstand anoxia.

In 1958 Cross, Tizard and Trythall reported in full some experiments earlier described in summary (Cross, Tizard and Trythall, 1955), which were performed to investigate the ability of the newborn baby to weather anoxia. It has already been noted

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that Himwich et al. (1942) had suggested that anaerobic metabolism was the main method of maintaining energy and heat production in anoxic newborn babies and animals. Cross and his colleagues proposed to investigate the response of the newborn infant to the very mild hypoxic stimulus caused by giving 15% oxygen. It was thought that the excretion of carbon dioxide in the expired air might be used as an index of the amount of anaerobic metabolism, on the supposition that lactic acid produced by the anaerobic breakdown of glucose would displace carbon dioxide from the bicarbonate in the extra cellular fluid. It was suggested that the carbon dioxide would be excreted in the expired air.

The result of giving 15% oxygen was a significant fall in oxygen consumption ". . . the extent of which, 16.9% less than the value in air, came as a complete surprise." Although the results for carbon dioxide production were less clear cut there was no rise in carbon dioxide excretion such as would be expected from anaerobic metabolism, but a significant fall which amounted to 6.6% in full term infants. Calculation based on the fact that carbon dioxide production fell showed that any anaerobic metabolism was far from sufficient to compensate for the decline in aerobic metabolism. It was concluded that in the mild hypoxia caused by 15% oxygen the rate of metabolism was lowered and not maintained by anaerobic metabolism, and that the fall in oxygen consumption was not due to a fall in body temperature.

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Brodie, Cross and Lomer (1957) showed that heat production, like oxygen consumption, was less when infants were breathing 15% oxygen. It must be noted that this was a very mild anoxic stimulus, equivalent for example, to an altitude of 8,000 feet and infants breathing 15% oxygen are, in general, not cyanosed.

Differences between babies, adult men and large animals.

Prior to this ". . . most stimulating paper" (Dawes, 1959), most physiologists had believed that oxygen consumption was independent of the inspired gas at least until the latter fell so far as to seriously endanger life and Dawes (1959) indicated some of the reasons for this belief.

1). Several workers cited by Cross et al. (1958) and Acheson, Dawes and Mott (1957) provided data for the conclusion of van Liere (1942) that gaseous metabolism was independent of the variation in atmospheric pressure. McCance and Widdowson (1957) stated that "it is generally agreed there is no reduction in oxygen consumption when the pO_2 in ambient air falls even to the low levels met with at very high altitude." This is true for men in basal or near basal conditions up to about 20,000 ft. (where the pO_2 approximates to that in 8% oxygen at atmospheric pressure). Although the arterial oxygen pressure falls there is a sustained increase in alveolar ventilation which maintains tissue oxygen supply.

2). In vitro most enzyme systems concerned with aerobic respiration have the ability to accept oxygen in solution at partial pressures as low as 5 mm. Hg.

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3). According to most workers oxygen consumption is not lowered in cyanotic congenital heart disease. Several groups of workers have studied the oxygen consumption in adults with cyanotic congenital heart disease. Bing, Vandam, Handelsman, Campbell, Spencer and Griswold (1948) found that in 30 patients with Fallots Tetralogy who had an arterial oxygen tension of 30-60 mm. Hg. (% oxygen saturation of 57-90) the basal metabolic rate was either markedly reduced or at the lower limits of normal. However the expected correlation between the basal metabolic rate and oxygen tension was not seen. Davison, Armitage and Arnott (1953), Burchell, Taylor, Knutson and Wood (1950) and Ernsting and Shephard (1951) examining patients with hypoxia due to congenital heart disease found that the basal metabolic rate was not related to the degree of hypoxaemia. However the degree of oxygen saturation in their subjects was in the range of 62-95% which is much less than the patients mentioned by Bing et al. (1948).

4). In adult dogs also experiments have been consistent with a hypothesis that oxygen consumption is not lowered until the equivalent of 6% oxygen is breathed.

Cordier and Mayer (1935) showed that on acute exposure to low oxygen tensions the oxygen consumption of adult dogs did not fall until death was imminent when they were breathing oxygen concentrations of about 6%. In the experiments of Lewis and Gorlin (1952), and Gorlin and Lewis (1954) the oxygen consumption of adult dogs at room temperature was studied;

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oxygen consumption was well maintained until the arterial oxygen saturation fell to about 40% which occurred when they were breathing oxygen concentrations of from 2.5 - 4.0%. They gave six other references to similar findings. Harrison and Blalock (1927) came to similar conclusions. Doi (1921) showed that oxygen consumption in the cat was unaffected by breathing 13.3% O_2.

The maximum as distinct from basal and intermediate levels of oxygen consumption is limited at altitude and Pugh (1958) showed that maximum oxygen consumption was slightly diminished at 7,000 feet. Recently the lay press reported poorer performances by athletes training at Mexico City for the Olympic Games. Here the altitude is 7,575 feet, which corresponds to an oxygen concentration of about 15.5% O_2. The slower times in long distance races were predicted by Pugh (1965).

The above work refers entirely to larger animals and McCance and Widdowson (1957) indicated some of the differences in the way large and small mammals react to hypoxia. In adult large animals (e.g. cats and dogs) oxygen consumption does not usually fall until death is imminent and they respond in a very different way from smaller animals, principally rodents, that have been investigated. It is now clear that the effect of environmental temperature is important.

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Effects of hypoxia on small animals.

In rabbits Ogata (1923) found that oxygen consumption fell below control levels as the concentration of oxygen breathed was lowered below about 12%. However in the same animals Hamon, Kolodny and Mayer (1935) found that the oxygen content of inspired gas could be reduced to about 8% without a fall in oxygen consumption at an atmospheric temperature of about 15-25°C. In mice Chevillard and Mayer (1935) showed that at an environmental temperature of 20-21.5°C oxygen consumption fell by about 6% in 14.5-14.7% oxygen. In 13.6% oxygen, oxygen consumption in the same subject fell by a much greater amount; there was also a fall in carbon dioxide excretion. Below these values for oxygen concentration the depression in metabolism was roughly proportional to the amount of hypoxia. (Chevillard and Mayer (1935) mentioned the interesting fact that similar hypoxia depresses the oxygen consumption of plants.)

Lintzel (1931) found that when rats were exposed to air at low pressure (450 mm. Hg; pO_2 equivalent to 12.5% O_2 at atmospheric pressure) there was a marked fall in oxygen consumption at temperatures below 29°C, but at higher temperatures there was a slight increase in oxygen consumption. Similarly Flückiger (1956) found that 10% oxygen caused a fall of 30% in oxygen consumption. But Blood, Elliott and D'Amour (1946) found that a similar decrease in oxygen consumption in rats did not occur until they were breathing the equivalent of 4.7% oxygen (Environmental temperature

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not stated). However at an environmental temperature of 18-20°C Blood, Glover, Henderson and D'Amour (1949) found that oxygen consumption fell at an equivalent of 11.7% oxygen.

The work of Cross et al. (1958) on newborn babies showed that hypoxia lowered $\dot{V}\ O_2$. This was an entirely new concept, at least in the neonatal field and was followed by much fruitful work on experimental animals. Their observations were very soon confirmed by Acheson, Dawes and Mott (1957) in foetal lambs, Moore (1956) newborn dogs, (1959) kittens and Hill (1959) kittens and adult guinea pigs (and by other workers mentioned in Discussion), who all confirmed that in newborn or small adult animals the oxygen consumption was lowered by hypoxia rather more severe than that used by Cross et al. (1958).

Reasons for the importance of environmental temperature.

In 1959, Hill published results on the effect of hypoxia on newborn kittens and adult guinea pigs which provided an explanation of the apparent marked differences in the response of oxygen consumption of large and small animals to hypoxia. She showed that in both newborn kittens and adult guinea pigs (which are approximately the same size) response to hypoxia depended on environmental temperature. At a neutral temperature, oxygen consumption was unaffected by reducing the oxygen concentration in the inspired gas as far down as 10%. Below the neutral temperature range however, at 26°C for kittens and at 20°C for guinea pigs, both species showed a fall in oxygen consumption of roughly 50% when they were given 10-12% oxygen.

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The apparent differences between the large and small animals and the conflicting reports about small animals can be explained by the fact that moderate hypoxia (10-12% oxygen) causes a reduction in oxygen consumption only if the animal is consuming oxygen at a rate greater than the basal rate. Whether or not an animal is metabolising faster than the basal rate depends partly on whether it is above or below the critical environmental temperature, which differs for different species. Rats, mice and guinea pigs are well below their critical temperatures at ordinary room temperatures but dogs and clothed adult men are not. Hill showed that newborn kittens and similarly sized adult guinea pigs have approximately the same sort of response to hypoxia.

This taken alone does not explain the increased ability of the newborn to withstand anoxia or why they should have continued in Boyle's "exhausted receiver" for "three times longer than adult animals of that bigness would have done." One factor is that because of their greater thermal insulation adult animals have a lower critical temperature than newborn animals of similar size and if the metabolic response to cold is abolished by hypoxia newborn animals will cool more rapidly. When newborn and adult animals of the same species are compared, newborn animals will cool much more rapidly partly because of their larger surface area to weight ratio. Hill (1959) cited work which showed that in adult small mammals and newborn animals the lower the body temperature the longer the survival without oxygen until low body

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temperature itself proved fatal (a Q10 effect). Newborn rats survive cooling to lower body temperatures than do adult rats (Adolph, 1948) and the lethal temperature becomes higher with increasing age (Adolph, 1951).

If the body temperature is not free to fall because the animal is in a warm environment, the ability to survive without oxygen is much less. Gellhorn showed in 1937 that mice and rats exposed to 8.1% oxygen exhibited a fall in body temperature at room temperatures. If the fall in body temperature was prevented by maintaining a high environmental temperature, 37°C, fewer animals survived given exposure to hypoxia than at room temperature. This reflects the advice of Paul Bert (1870) to obstetricians performing caesarean section when he remarked that warming instead of cooling the infant might hasten its death. Blood et al. (1949) found that survival rate was much greater in a group of rats at an environmental temperature of 20°C exposed to a simulated altitude of 32,500 ft. (about 4% oxygen) than a similar group at 35-37°C. Even at simulated altitudes of 40,000 ft. some rats survived when they were at environmental temperatures of 20°C although all perished in the group exposed to environmental temperatures 35-37°C at or before 32,500 ft.

In the light of Hill's work (1959) some of the experiments on hypoxia in larger animals are better understood. Hemingway and Nahas (1952) found a transient fall in oxygen consumption in adult dogs in a warm environment, 24°C, when they were given 12% oxygen but a much greater though again transient decrease in oxygen consumption when 8% oxygen was given in a cool environment, 12°C, when they were shivering.

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In cats the effect of hypoxia on oxygen consumption was the same as in dogs. In shivering cats the data of Hemingway and Birzis (1956) showed that oxygen in concentrations of 13-8% in the inspired gas decreased oxygen consumption to basal levels and abolished shivering. The effect of hypoxia on non shivering decerebrate cats was different and oxygen consumption did not fall until the concentration of oxygen breathed was reduced to 6%.

Environmental temperature and the work of Cross et al.(1958)

The work cited above showed clearly that mild hypoxia only lowered oxygen consumption if the animal was in a cool environment. It seems likely that the same would be true of babies. Cross suggested (1959) that the infants studied by him and his colleagues were in a cool environment, although the environmental temperature was not measured, and that the fall in oxygen consumption observed was due to inhibition of the metabolic response to cold. It is now necessary to consider some of the evidence that newborn infants do have an increase in oxygen consumption in a cool environment.

Metabolic response to cold in infants.

Little was known about the final control mechanisms for temperature regulation in the first week of life in the human infant until the work of Brück who collected together much of his earlier published work in his paper of 1961. Brück examined both newborn and premature infants from the first few hours of life onwards and measured in an open circuit apparatus oxygen consumption and carbon dioxide production over

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periods of five minutes. This contrasts with the earlier work of Day (1943) and Karlberg (1952) who both used, for methodological reasons periods of about half an hour. Brück considered that it was necessary to use shorter periods because of intermittant restlessness which caused a slight temporary rise in metabolic rate.

He found values for basal metabolic rate in full term infants that were similar to but slightly lower than those of Benedict and Talbot (1915) and than those of Cross et al. (1957). He suggested that his values might be lower because they were obtained over a shorter time interval than was used by the earlier workers and were not subject to slight increases caused by restlessness. However this may not be the only reason because the infants studied by Cross for example over 10 minute periods were quite inactive. Hill and Rahimtulla (1965) suggested that the observations of the earlier workers might not have been made at sufficiently high environmental temperatures.

Brück also showed that exposure of both full term and premature infants to cool air provoked increases in oxygen consumption even during the first few hours after birth and that the skin vessels were able to produce marked vasoconstriction immediately after birth. The increase in oxygen consumption in a cool environment was quite considerable and in both full term and premature infants the oxygen consumption increased by about 100% above basal levels on exposure to 23°C.

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Such an increase is considerably greater than that achieved by adults under the same conditions who show no rise at all or at the most only a 25% increase. The greater metabolic response to cold enables the newborn infant to compensate for its relatively greater heat losses due to less favourable surface volume index and smaller body shell.

The earlier suggestion of Day (1943) that the skin might have "a thermostatic control" was considerably amplified. Brück showed that oxygen consumption increased with much smaller changes in the skin temperature and at much higher skin temperatures than in adults. This is amplified in the discussion page 137 where some of Brück's findings on the ability to produce maximum skin vasoconstriction very soon after birth are also mentioned.

Since the work of Brück a number of other authors have described the increase in oxygen consumption in a cool environment which occurs in infants (Oliver and Karlberg, 1963; Levison and Swyer, 1964; Hill and Rahimtulla, 1965; Adamsons, Gandy and James, 1965). Some of their experiments will be described later (see Discussion).

Nature of Metabolic Response to Cold.

There are three possible mechanisms by which oxygen consumption may be increased in a cold environment:-

1). Voluntary movement caused by cold discomfort.

2). Involuntary or tonic muscular activity which at first may be detectable only by electromyography but if the cold stimulus persists progresses to rhythmic visible shivering.

3). Non shivering thermogenesis.

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Heat production in the newborn and in the adult.

Normally in adult animals and in the adult man thermogenesis in the cold in the absence of bodily activity is brought about chiefly by shivering. In the experiments quoted by Hemingway (1963) in which the environmental temperature was slowly lowered in an effort to detect non shivering thermogenesis only small and almost insignificant increases in oxygen consumption were observed in the absence of shivering. In newborn animals however the position is somewhat different. They are able to increase their oxygen consumption in a cold environment without visible shivering and this factor has been commented on by most of the workers in this field, for example Hill (1959) and Blatteis (1964).

Newborn guinea pigs increase their oxygen consumption in the cold without electromyographic evidence of muscle activity (Brück, 1964) and Dawes and Mestyan (1963) showed that the newborn rabbit could increase its oxygen consumption in a cold environment even when totally paralysed by Gallamine, a neuromuscular blocking agent.

Although newborn animals do not usually shiver, in certain circumstances they can do so, (Blatteis, 1964, Dawkins and Hull, 1964), and some of the more "mature" newborn animals such as piglets and lambs shiver readily.

Newborn infants behave in a similar manner to newborn animals. The oxygen consumption of the newborn infant can increase in a cool environment without shivering, (Mordhorst, 1933; Brück, 1961; and Adamsons, 1965). Although the newborn infant is

Introduction (cont'd).

usually active and cries at lower environmental temperatures an increase in oxygen consumption can occur without activity and without shivering, (Hill and Rahimtulla, 1965). Babies also resemble newborn animals in that they can shiver but do not usually do so until they are exposed to relatively low environmental temperatures, for example naked at 24°C and even then shivering does not appear to cause much further increase in the oxygen consumption, (Hill and Rahimtulla, 1965). One can assume that non shivering thermogenesis is prominent in newborn animals but that in older animals it becomes less important (Brück, 1964).

Thermogenesis in the cold adapted rat.

Before discussing the role of non shivering thermogenesis in the newborn animals and infants it is necessary to mention some work on cold acclimated adult rats.

On the assumption that curarisation suppresses shivering but leaves non shivering thermogenesis unimpaired it is possible to separate the two. Cottle and Carlson (1954; 1956) investigated the metabolic response to cold of groups of cold acclimated and non acclimated rats. When both groups were totally paralysed by curarising agents and subjected to a standard cold stress they found that non acclimated rats produced only a slight rise in oxygen consumption but that cold acclimated rats produced heat at double their basal rate. This implies that non shivering thermogenesis plays a prominent part in maintaining heat production in cold adapted rats.

Introduction (cont'd).

The mechanism of cold acclimation was extensively reviewed by Smith and Hoijer (1962); they mentioned the increase in the relative size of the liver and viscera and the marked increase in the excretion of nor-adrenaline derivatives. Perhaps the most interesting aspect of cold acclimation in the rat is the metabolism of a pad of brown fat between the scapulae. This tissue increases both in amount and metabolic activity during cold acclimation, when its heat production increases 3 to 4 times and "may contribute significantly to the heat requirements of the animal." (Smith, 1963).

Smith (1963) found that there was an immediate thermal response from brown fat both when the animal was placed in a cool environment and when nor-adrenaline was infused intravenously. It will be seen that there are surprising similarities between the cold adapted adult rat and the newborn of various species.

Thermogenesis in the newborn.

Dawes (1965) has recently reviewed the subject of heat production in the cold in the newborn. In describing the role of sympathetic amines he pointed out that the response of newborn animals to nor-adrenaline differs considerably from that of adults. In the normal adult animal there is little increase in oxygen consumption when nor-adrenaline is given intravenously but when it is given in both pharmacological and physiological doses to newborn kittens, rabbits and babies it causes an increase in oxygen consumption which may mimic the metabolic response to cold. Infusion of

Introduction (cont'd).

pronethalol blocks the action of intravenous nor-adrenaline in newborn rabbits but does not impair the metabolic response to cold (Hull, 1964). This implies that the metabolic response to cold cannot be the result of the secretion of nor-adrenaline into the blood stream, but as Dawes suggested it could still be due to the liberation of nor-adrenaline at the end organ in a situation where pronethalol could not penetrate.

Brown fat in animals.

It appears then that the response of newborn animals to intravenous nor-adrenaline resembles that of adult cold adapted rats. The link between the two is partly due to the work of Smith (1963) who mentioned "A new consideration" in the thermal control in the newborn and described briefly the relatively large mass of brown fat in the newborn mouse. Smith and Hoijer (1962) pointed out the presence of brown fat in a wide variety of newborn animals including man.

The role of brown fat in the thermogenesis of newborn animals has been investigated by Dawkins and Hull (1964), Hull and Segall (1965 a b,c) using rabbits and by Brück (1964) using guinea pigs. The subject was reviewed by Hull (1966). In newborn rabbits, Dawkins & Hull (1964) found that brown adipose tissue was situated mainly in the inter scapular region and round the neck, as in the newborn mouse, and comprised about 5.5% of the body weight. It was liberally supplied with nerves and blood vessels and diminished rapidly in size in the first week of life to be replaced by white fat. In experiments designed to investigate the role of the brown fat in the metabolic

Introduction (cont'd).

response to cold, the subcutaneous temperatures over the brown fat and over the lumbar muscles, and the deep colonic temperature were measured together with the oxygen consumption, in the warm and cool environments and in response to intravenous nor-adrenaline and hypoxia.

In a warm environment the three temperatures were equal but on exposure to cold environment there were marked changes. The rectal and lumbar subcutaneous temperatures rapidly fell but the subcutaneous temperature over the brown fat remained at its initial high level. At the end of 30 minutes of exposure to cold the temperature over the brown fat was more than $1^{o}C$ higher than the deep colonic temperature and more than $2^{o}C$ higher than the lumbar subcutaneous temperature. The oxygen consumption was 3 times the basal level. The temperature of the anterior abdominal wall close to the liver was also measured and found to be lower than the colonic temperature. There were similar changes when nor-adrenaline was infused intravenously which were blocked by the prior administration of pronethalol. In vitro it was found that the metabolic activity was as high in brown fat as in newborn cardiac muscle and considerably higher than that of liver, muscle or any other tissue in the body.

They concluded that the large mass of brown fat relative to the body weight of the animals, its rich blood supply, its high in vitro metabolic rate and the fact that the subcutaneous temperature over the brown fat was higher than any other recorded site all indirectly

Introduction (cont'd).

suggested that it is probably the major site of non shivering heat production in newborn rabbits.

Other potential sites for non shivering thermogenesis must be mentioned. Scopes and Tizard (1963) suggested that the liver was a site of heat production in young kittens. In kittens subjected to a functional evisceration there was a reduction in basal metabolic rate. There was also a reduction in the increase in oxygen consumption during the infusion of intravenous nor-adrenaline. It is interesting that Aschoff (1960), quoted by Smith and Hoijer (1962) found that the splanchnic visceral region in the adult contributes about 37% of the resting heat production. Dawes and Mestyan (1963) found that the cardiac output of newborn rabbits increased in the cold and this must contribute in part to the heat production and increased oxygen consumption.

In the experiments of Dawkins and Hull (1964) the subcutaneous temperature over the lumbar muscles was chosen because of its proximity to a site where the heat production due to shivering, if any, might be recorded. They observed that even when shivering did take place there was little increase in subcutaneous temperature.

Brück (1964) performed electromyographic (E.M.G.) and oxygen consumption measurements on newborn guinea pigs and studied the amount of muscle activity in more detail. It was found that in animals of a few days old, who were in a cool environment, the oxygen consumption rose to about 2 or 3 times basal level and that not only was there no visible shivering but there

Introduction (cont'd).

was very little E.M.G. activity. The findings in animals in the second week of life were in marked contrast; in the second week there was a large increase in muscular activity on cooling and there was visible shivering. Brück also observed that there was a marked increase in blood flow over the interscapular fat pad in a cool environment but this diminished in the second week of life.

Possible role of brown fat in babies.

According to Brück (1964) it has long been known that brown adipose tissue was present in the newborn infant; and Aherne and Hull (1964) described its location predominantly in the interscapular region and in the floor of the posterior triangle of the neck. However the amount per kilogram was considerably less than in the newborn rabbit. The role of brown adipose tissue in thermogenesis in the baby has not been extensively investigated. It has been pointed out that the response of the newborn infant to intravenous nor-adrenaline is similar to that of newborn animals (Karlberg, Moore and Oliver, 1963), and there is also an increased excretion of catechol amines in a cool environment, (Sandler, Norman, Ruthven and Moore, 1961; Stern, Lees and Leduc, 1965). Dawkins and Hull (1965) demonstrated that in newborn infants in a cool environment there was a rise in plasma glycerol without an equivalent rise in fatty acids. This response would be expected from the breakdown of brown fat. Silverman, Zamelis, Sinclair and Agate (1964) in a paper entitled "Warm nape of the Newborn" measured the skin temperature in newborn infants before and after exposure for 1 hour to a cool environment. It was found

Introduction (cont'd).

that the fall in skin temperature was greatest over the extremities and least over the trunk, as is well known, but over the nape of the neck the fall in skin temperature was less than the fall in colonic temperature. However the difference between the fall in the skin temperature and the fall in the colonic temperature was not statistically significant. It is interesting to note that the nape of the neck is where the brown fat is concentrated in the newborn baby as in other newborn animals.

This evidence does no more than support the suggestion that brown fat may be an important source of thermogenesis in the baby.

Mechanism of action of hypoxia on the metabolic response to cold.

This aspect was recently reviewed by Dawes (1965). Both shivering and non shivering thermogenesis are important in the metabolic response to cold and the effects of hypoxia on these two processes appear to differ slightly. In the newborn infant shivering is rarely seen except when the naked infant is exposed to environmental temperatures of something less than 24°C and as mentioned there is much evidence that newborn animals increase their oxygen consumption in the cool without shivering. The effects of hypoxia on shivering will be briefly mentioned and the effects of hypoxia on non shivering thermogenesis will be discussed.

Hypoxia and shivering.

Cross, Dawes and Mott (1959) found that shivering in newborn lambs was abolished by hypoxia and Mott in 1963 showed that electrical stimulation of the nerve

Introduction (cont'd).

leaving the chemoreceptors temporarily abolishes shivering. Stimulation of the chemoreceptors is therefore probably the mechanism by which hypoxia acts on shivering.

Shivering appears to be more resistant to prolonged hypoxia than is non shivering thermogenesis. In adult dogs Hemingway and Nahas (1952) found that hypoxia abolished shivering provoked by exposure to a cool environment (12°C) and the oxygen consumption returned to basal values. However over the next hour both shivering and oxygen consumption gradually rose to control values which were about 50% greater than in a warm environment. The experiments of Blatteis (1964) permit a similar conclusion. He found that 10% oxygen always caused an immediate fall in oxygen consumption in newborn rabbits in a cold environment but when hypoxia was continued over 4 hours oxygen consumption gradually rose and was usually accompanied by visible shivering which was absent when the rabbit was first exposed to the low temperature. Hill (1959) did not find any change in oxygen consumption in a newborn kitten exposed to 10% oxygen in the cool for 1½ hours (see her Fig. 5). However in this animal shivering was not seen.

Hypoxia in the newborn: Hypotheses.

The position is different where the increase in oxygen consumption is not due to shivering. Cross (1958) suggested some possible mechanisms by which the hypoxic newborn infant might lower oxygen consumption. The simplest hypothesis is that all the cells in the body participate in the lowering of oxygen consumption and

Introduction (cont'd).

this suggestion has not been disproved. However Cross also suggested two other speculations from comparative physiology and mentioned two types of animals which are specially adapted to long periods of low oxygen usage.

In the diving seal it is now known that there is a very marked constriction of the aorta and the major arteries except for those supplying the brain and heart, (Robin, 1965). It was thought possible that there might be a similar vascular redistribution in the anoxic baby. However Moore (1959) showed that in kittens an injection of hexamethonium, a ganglion blocking agent, modified but did not alter the general character of the response of oxygen consumption to hypoxia. He considered that this rendered vascular redistribution an unlikely theory.

In hibernating animals there is a special gland composed of thermogenic brown fat which is highly metabolically active, (Smith and Hoijer, 1962), and it maintains a more euthermically normal level of metabolism than does any other tissue of the body. Smith and Hock (1963) suggested that brown fat might be a site of heat production during arousal from hibernation. Smith (1962) on the basis of work on the cold adapted rat suggested also that brown fat might warm cool blood from the periphery and selectively keep warm essential deep structures such as heart and brain in hibernating animals. The suggestion that the physiology of hibernants might provide a parallel to the effect of anoxia on newborn animals has been shown by recent work (Dawkins and Hull, 1964) to be remarkably accurate prediction.

Introduction (cont'd).

Hypoxia and brown fat.

It is now known that brown fat is an important source of non shivering thermogenesis in newborn animals and possibly also in the newborn infant; some of the evidence for this has been mentioned. Dawkins and Hull (1964) have shown that in a cool environment the subcutaneous temperature over a large interscapular deposit of brown fat in the newborn rabbit was considerably higher than the colonic temperature or the subcutaneous temperature elsewhere. When the newborn rabbit was exposed to hypoxia (5% oxygen), the differences in temperature were abolished, and there was a sharp fall in all three temperatures which was greatest over the brown fat; here the subcutaneous temperature fell to below colonic temperature and almost to the level of the subcutaneous temperature over lumbar muscles. The oxygen consumption fell to basal levels. When air was given the temperature over the brown fat immediately rose to control levels and simultaneously the oxygen consumption rapidly increased. Colonic and subcutaneous temperatures continued to fall for a short time before increasing also to levels similar to the controls in air.

This work shows that thermogenesis from brown fat is very sensitive to hypoxia and that brown fat contributes to a considerable extent to heat production. It is suggested that this is at least one of the most likely explanations for the effect of hypoxia on the metabolic response to cold. Exactly how hypoxia inhibits the heat production of brown fat is not known but the increase in blood flow through brown adipose tissue provoked by intravenous nor-adrenaline is not

Introduction (cont'd).

greatly altered by 10% O_2 (Hull, 1966). In newborn infants exposure to 10% oxygen for short periods does not affect the urinary catechol amine excretion. (Stern, Leduc and Lind, 1964).

Although chemoreceptor stimulation is important in the effect of hypoxia on shivering it does not appear that this is the case in non shivering thermogenesis and Blatteis (1964) showed that bilateral section of the carotid sinus and/or the vagus nerves did not effect the immediate fall of oxygen consumption caused by hypoxia and he concluded that the fall could not be attributed to chemoreceptor stimulation. (Blatteis also showed that the metabolic action of intravenous nor-adrenaline and isoprenaline was reduced but not suppressed by 10% oxygen at 35°C and 25°C).

Introduction (cont'd).

ANOXIA AND HYPOXIA IN A WARM ENVIRONMENT.

The work described so far relates chiefly to the effect of cooler environments on the ability to withstand anoxia, and the importance of physical factors in lowering metabolic rate. The effect of biochemical factors in environments where the temperature is controlled and the subject is kept warm will be discussed.

The effect of hypoxia in a warm environment.

Cross, Dawes and Mott (1959) showed that there was a fall in oxygen consumption in the lightly anaesthetised lamb in a warm environment when given oxygen in concentrations of less than 12%. In the same paper it was shown that hypoxia had a greater effect on the basal metabolic rate of lambs older than 1 day which had achieved the usual postnatal rise in basal oxygen consumption than in 1 day old lambs which had not. Thus in the lamb the newly acquired increase in basal metabolic rate is more susceptible to hypoxia as Mott (1963) has indicated.

The effect of anoxia in a warm environment.

Dawes (1960) postulated that there must be at least two factors in the ability of the newborn to withstand anoxia and these he designated the "tissue factor" and the "circulatory factor". The evidence shows that the respiratory centre can continue functioning while anoxic for a surprising length of time in the absence of the circulation (20 minutes in the newborn rat), but that in the presence of circulation gasping continues for about twice as long (Himwich et al., 1942 in rats; and Dawes, Jacobson, Mott and Shelley, 1960, in foetal monkeys).

Dawes and his colleagues designed a series of experiments to investigate the "circulatory factor". In these experiments the environmental temperature was

Introduction (cont'd).

held constant and lowered body temperature as a factor in tolerance to anoxia was eliminated by keeping the body temperature as near to the normal as possible.

Dawes, Mott and Shelley (1959), Dawes, Jacobson, Mott, Shelley and Stafford,(1963) and Stafford and Weatherall (1960) showed that there was a marked fall in cardiac carbohydrate concentration during anoxia and that the survival time was directly related to the initial cardiac carbohydrate concentration.

In foetal lambs there was a direct correlation between the ability to survive anoxia and the carbohydrate concentrations in the heart. As term approached both the cardiac carbohydrate and the ability to withstand anoxia decreased. The younger foetus survived anoxia longer because of the greater carbohydrate concentration at the beginning of anoxia and because it was depleted less rapidly. After birth the same relationship persists. In the newborn rats, rabbits, guinea pigs and monkeys there was a direct relationship between the initial cardiac carbohydrate concentration and the time of the last gasp while breathing nitrogen or during asphyxia.

If the cardiac carbohydrate was reduced by previous fasting or anoxia the survival time also was reduced. With increasing age the ability to tolerate anoxia and the cardiac carbohydrate both diminished. The ability of the species which are less mature at birth to survive anoxia for longer periods is also explicable on the same basis. Shelley (1961) has shown that the cardiac carbohydrate is highest in the most immature species such as rats and lowest in the most mature species such as guinea pigs.

Introduction (cont'd).

The ability to tolerate asphyxia at lower environmental temperatures when the body temperature is free to fall, is also/partly explicable on this hypothesis since it was found that at low temperatures the cardiac carbohydrate was depleted less rapidly than at higher temperatures.

The "circulatory factor" was further investigated in a series of experiments which showed that intravenous alkali and glucose during asphyxia maintained circulation and prolonged the duration of gasping in asphyxiated foetal lambs and Rhesus monkeys.

In addition to the high cardiac carbohydrate concentration which forms part of the "circulatory factor" Dawes also suggested (1960) that a "tissue factor" might be important and some of the evidence which supports this is mentioned by Mott (1961) in her review of this subject.

Introduction (cont'd).

CLINICAL STUDIES IN ASPHYXIA.

The evidence of the ability of the newborn infant to survive anoxia is of course indirect and controlled experiments are naturally not available. However there are some valuble isolated cases of birth of infants after death of their mothers and more importantly many studies relating the degree of asphyxia after birth to the latter development of the child.

Survival after maternal death.

Harvey (1651b) wrote "A certain woman here amongst us (I speak knowingly) was (being dead over night) left alone in her chamber, but next morning an infant was there found between her legs which by his own force wrought his release. Gregorius Nymanus has collected certain examples of this nature out of approved authors." In a conference on anoxia of the newborn infant, (Cross, Lelong and Smith, 1953) it was suggested that after 20 to 40 minutes of anoxia there would be irreversible changes in the cerebral cortex, whether anoxia occurred in utero or immediately after birth. Hellman (1953) mentioned two personally observed cases in which normal foetuses were delivered in excellent condition 20 minutes after the sudden death of the mother during labour. There was no prodromal asphyxia and one assumes that these infants had not been anoxic in utero.

Bullough (1958) described a male infant who survived 20 minutes intrauterine asphyxia and 10 minutes neonatal asphyxia. His first attempt to breathe was 40 minutes after birth yet he appeared normal at the age of 1 year, and won a baby show at 9 months. This was not an example of postmortem caesarean section and the mother made a normal recovery. Even more remarkable

Introduction (cont'd).

cases are described by Young (1944) in his chapter on postmortem caesarean section.

Perhaps the most amazing case which he accepted as authentic was that of Cleveland (1878). In this case the mother died of convulsions and caesarean section was performed after she had been dead for an hour. The child was asphyxiated but after one hour was "fully restored" and appeared later to make a complete recovery.

Follow up studies on babies with asphyxia neonatorum.

Definitions.

The terms asphyxia, anoxia and apnoea are frequently used and it is important to be precise about their meanings. Anoxia designates the absence of supply of oxygen to the tissues and asphyxia a condition of anoxia combined with an increase of carbon dioxide tension in the blood and tissues. Apnoea is taken to mean not breathing.

There are a number of studies relating the severity of asphyxia at birth to subsequent development, intelligence and behaviour tests. The classicalaccount is that of Little (1862).

Drillien (1965) recently reviewed the effects of neonatal apnoea on subsequent development and remarked that the development of infants with neonatal apnoea, compared with children without respiratory difficulties will depend on the primary cause of the failure to breathe rather than the presence or absence of this particular sign.

Drillien quoted work to show that if postnatal asphyxia was accompanied by foetal hypoxia and prematurity it was more likely to be associated with subsequent neurological defect.

Introduction (cont'd).

Foetal hypoxia at present is impossible to assess quantitatively and it is more convenient and equally valid for our purposes to consider the effects of postnatal asphyxia.

Arterial blood oxygen content.

Perhaps the most precise method of measuring anoxia at a given moment is to measure the blood oxygen saturation, but several groups of workers cited by Drillien (e.g. Apgar, Girdany, Mackintosh and Taylor, 1955) have found that there is no correlation between this factor and subsequent development. As Graham, Caldwell, Ernhart, Pennoyer and Hartman (1957) remarked the probable reason for this is that oxygen content changes too rapidly in response to too many factors to be of any practical assistance in long term evaluation.

Clinical evidence of asphyxia.

On the other hand some of the studies reviewed by Drillien have shown that there is a correlation between clinical evidence of neonatal asphyxia and subsequent development. Drillien considered that the study of Fraser and Wilkes (1959) gave the best indication of residual effects to be expected after postnatal asphyxia. In this study the degree of asphyxia was assessed by the delay in onset of respiration and crying.

In the infant with moderate asphyxia the first gasp occurred at 0 to 3 minutes and regular respirations were established in 3 to 5 minutes. In the severely asphyxiated group the first gasp was usually at 3 to 5 minutes and regular respirations were not usually established until more than 5 minutes and usually in more than 15 minutes. At the age of 7½ years the previously asphyxiated babies were compared with matched controls.

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Three of the 40 children in the severely asphyxiated group had definite or probable epilepsy, only one of those in the moderately asphyxiated group had possible epilepsy while there was no epilepsy in the controls. The whole of the asphyxiated group showed no difference from the controls in intelligence or personality but there was evidence of minor disorders in other fields, for example, perception testing.

A later study (Atkinson, Fraser, Lowit and Pampiglione, 1962) on the severely affected asphyxiated children of the study above, with some others added, showed that the electroencephalographs of the severely asphyxiated group, when they were six years old and when assessed by a neurologist who had no knowledge of the clinical history were not different from the controls. Of the 145 severely asphyxiated infants reviewed in the later survey cerebral palsy, epilepsy or nerve deafness were present in 10%.

Drillien was able to conclude ". . . from these various reports it would appear most likely that in the absence of foetal hypoxia that few maturely born infants who fail to breathe for 15 minutes or longer suffer gross damage, although minor impairment may be relatively common."

Baby and animal survival of asphyxia.

It is interesting to compare this conclusion with those of Fazekas et al. (1941) who found that rats survived 50 minutes and guinea pigs 7 minutes in pure nitrogen and of Dawes et al. (1963) who found that mature foetal lambs lived only six minutes in nitrogen. Certainly the newborn infant is less mature at birth than the lamb which is able to walk within a few hours.

Introduction (cont'd).

RECENT WORK WITH 15% OXYGEN IN BABIES.

In view of the work with newborn animals, (Hill, 1959 and others) which showed that the metabolic response to cold was reduced by relatively mild hypoxia, it seemed clear that in the pioneer experiments of Cross and his colleagues in 1958 the oxygen consumption had fallen in 15% oxygen because the babies were in a cool environment. It seemed probable that the metabolic response to cold had been inhibited by 15% oxygen and unlikely that the hypoxia had affected the basal metabolic rate. In 1959 Cross suggested that the metabolism of hypoxic infants must be investigated with more rigid control of environmental temperature.

Oliver and Karlberg (1963) designed experiments to evaluate the suggestion that in a cool environment babies would show a fall in oxygen consumption when breathing 15% oxygen but that it was unlikely that 15% oxygen would have any effect in a warm environment. Using an open circuit apparatus they found that in the cool environment the mean fall in oxygen consumption in infants breathing 15% oxygen was 18%. In a warm environment 15% oxygen did not lower oxygen consumption. There was no change in oesophageal temperature in 15% oxygen.

The results of Cross and his colleagues (1958) and of Oliver and Karlberg (1963) appeared to show quite definitely that the oxygen consumption of babies in a cool environment was very sensitive to hypoxia, and this conclusion appeared to fit well with animal work (but see later page 122). However it was decided to repeat their experiments using a closed circuit apparatus

Introduction (cont'd).

and this was the object of the work described here. When our work was begun it seemed highly likely that we would find a fall in the oxygen consumption of newborn infants in a cool environment when they were given 15% oxygen to breathe.

CHAPTER 2

APPARATUS

CONTENTS OF APPARATUS

THE CLOSED CIRCUIT.

CONTENTS OF APPARATUS CONT'D.

APPARATUS

The apparatus was designed and constructed at the London Hospital and has been the subject of a short publication (Cross, Hill and Rahimtulla, 1963). It is a new improved and enlarged version of that originally developed by Hill (1959) and was briefly described by Hill and Rahimtulla (1965).

The apparatus is shown in diagramatic form in Fig. 1. The baby lay in the water-jacketed metabolic chamber; the circuit gas was propelled by the pump through the gas flow meter and heat exchanger and after passing the thermo-couples recording the dry and wet bulb depression temperatures, entered the chamber. It circulated through the chamber containing the baby, then passed a second set of thermo-couples, and went through a carbon dioxide absorber and a cooling condenser to return to the pump. The volume of the circuit was maintained constant by the addition of oxygen via a tube situated near the intake side of the pump. The individual parts of the apparatus will be described in detail and for convenience of description it can be divided into two parts:

1). A closed circuit in which the infant lay and which was completely closed except for its connection to:-

2). A system for replacing and recording oxygen consumed.

THE CLOSED CIRCUIT.

The Metabolic Chamber and Water-jacket.

The chamber itself was basically an open ended perspex cylinder with its long axis horizontal; Fig. 2 gives an overall view. The sides but not the ends of

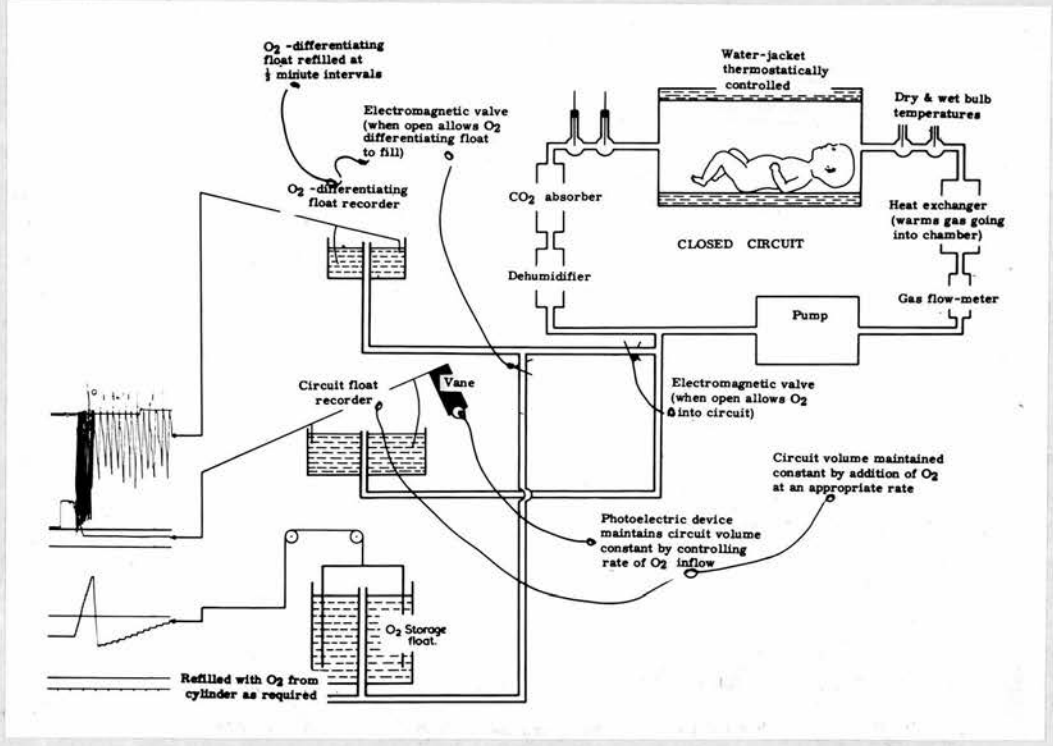


Fig. 1(a). Diagram of apparatus.

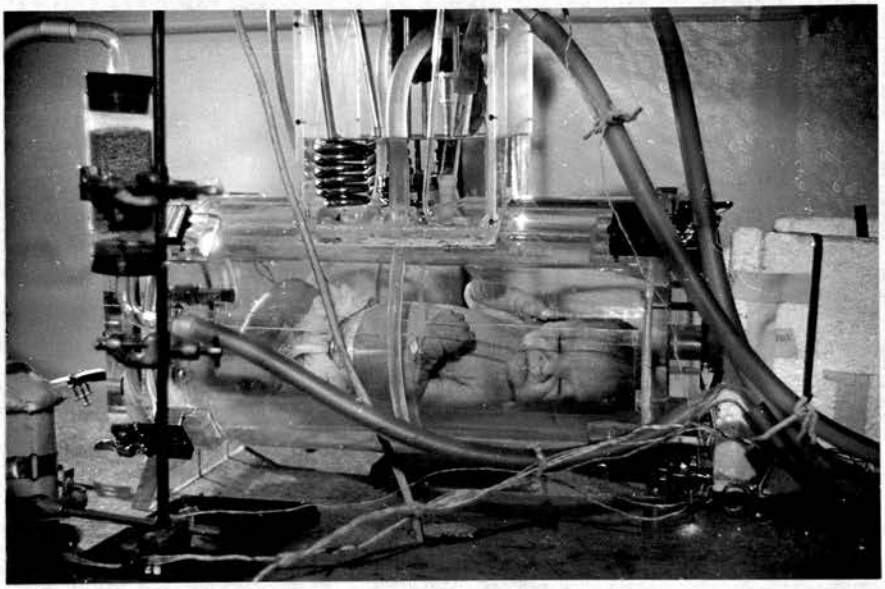


Fig.1(b)

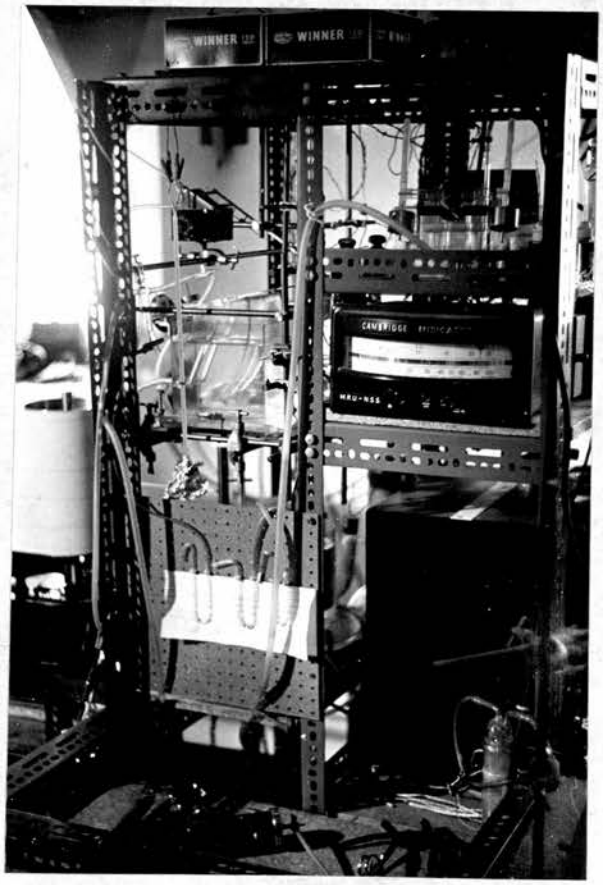


Fig. 1(c).

Fig. 1, b and c.
Photographs of
apparatus.

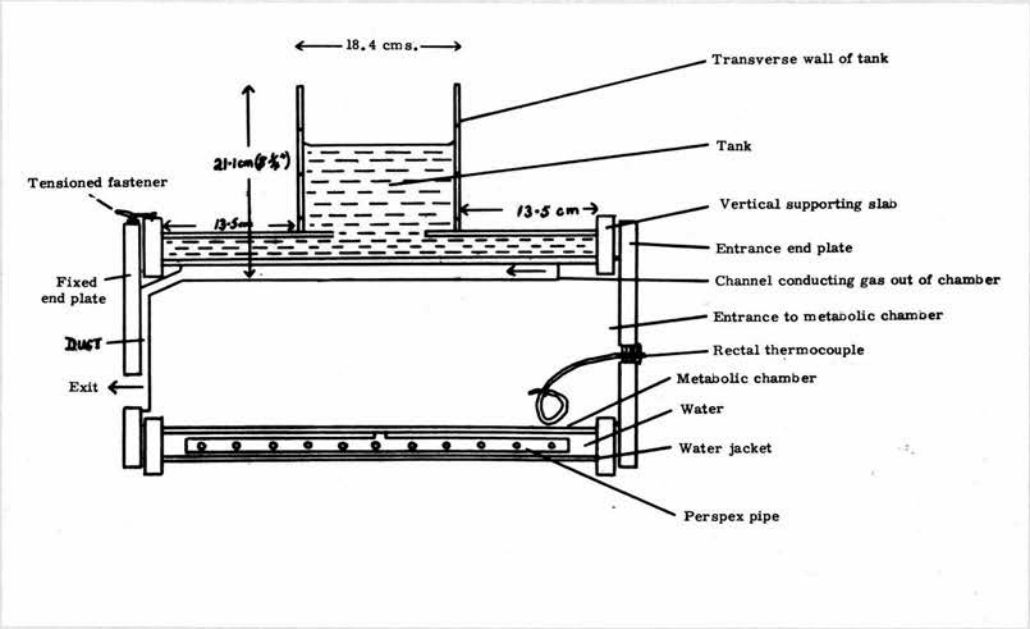


Fig. 2. Metabolic chamber:- Longitudinal section. The tank for the circotherm and the heaters is shown, and the aperture through which the water-jacket communicated with the tank. The circuit gas entered through an opening in the fixed end plate (not shown), passed to the entrance end of the chamber and was conducted along the channel in the direction indicated by the arrow, to a duct and out through exit aperture in the fixed end plate. The perspex pipe distributes water from the pump along the floor of the water-jacket.

Apparatus (cont'd).

the chamber were entirely surrounded by a similar cylindrical water-jacket. The chamber was closed at each end by two perspex end plates, one of which was used for access to the inside of the cylinder and was frequently removed, the 'entrance end plate', while the other was usually kept fixed in position, the 'fixed end plate'. The 'entrance end plate' was removed to allow the baby to be moved in and out of the chamber; the 'fixed end plate' carried openings for the incoming and outgoing circuit gas. The ends of the water-jacket and metabolic chamber cylinders were secured in two vertical supporting slabs of perspex.

The Entrance End Plate.

The relationship of the entrance end plate to the rest of the apparatus is shown in Fig. 2. It was a square of 1.9 cm. ($\frac{3}{4}$") thick perspex with rounded corners similar in shape to the fixed end plate (Fig. 3). It could be attached to the vertical supporting slab by four tensioned fasteners (Figs. 8 and 9). A gasket comprising a hard rubber O-ring was attached to the vertical supporting slab of the cylinders and the tensioned fasteners pressed the plate into contact with the gasket at the line marked G on the diagram to ensure a leakproof seal.

There were openings in the central part of the plate allowing communication with the baby lying inside the chamber. These were designed to allow rectal thermo-couple, ECG and EEG leads and intravenous tubing to be connected to the baby. Usually only the opening for the thermo-couple leads was in use and the others were closed. Two of the openings consisted of brass tubing screwed tightly into the perspex and the third was simply a 2 cm. diameter hole which could be closed by a rubber cork.

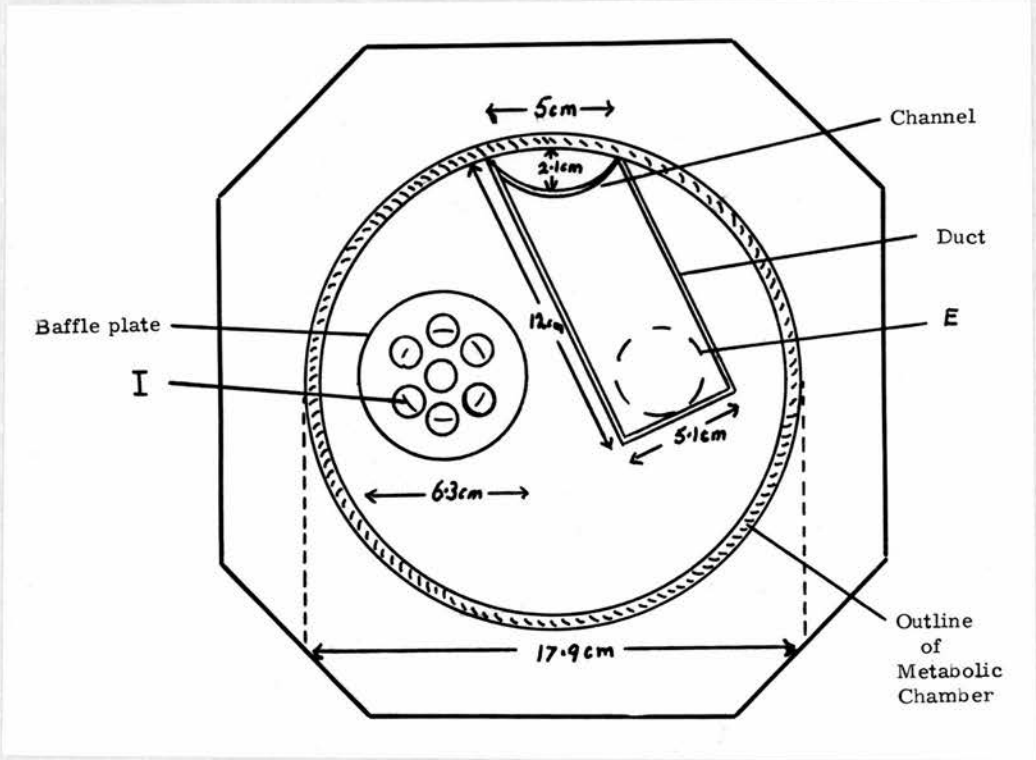


Fig. 3. Metabolic chamber: Fixed end plate, inner aspect.

This end plate was clamped onto the metabolic chamber and the side closest to the chamber is shown with plan views of the structures applied to this face of the end plate. The baffle plate was a perspex disc pierced with ½" diameter holes which deflected gas entering the chamber and prevented the infants head from blocking the opening. Gas entered through I. The duct which carried gas from the channel to the opening E for the out-going gas is demonstrated. The outline of the wall of the metabolic chamber has been superimposed on the end plate. The tensioned fasteners have been omitted, and the dimensions of the plate are shown on the next diagram.

Apparatus (cont'd).

To ensure a leakproof exit the thermo-couple leads were passed through wide bore thick walled soft rubber tubing which was sealed by two gate clips at right angles to each other. The latter compressed the soft rubber onto the leads.

The Fixed End Plate.

This was at the opposite end of the cylinder and was similar in size and shape to the entrance end plate. The inner (metabolic chamber) aspect is shown in Fig. 3, and the outer aspect in Fig. 4. It also was attached to the vertical supporting slab by tensioned fasteners and there was a similar gasket. It contained two apertures for the entry and exit of the gas and on the inner surface was part of a ducting system for routing outgoing gas. The relationship to the rest of the apparatus is shown in Fig. 2.

The opening through which gas entered is detailed in Fig. 5; gas enters through the brass tubing which is sealed into the perspex.

Baffle Plate. A disc of 0.3 cm. ($\frac{1}{8}$") thick perspex (Fig. 5) raised $\frac{1}{2}$" from the inner surface of the endplate covered the end of the brass tubing. The disc was pierced by holes 1.3 cm. ($\frac{1}{2}$") diameter (Fig. 5). It deflected the incoming gas and shielded the end of the tube from the infant. It also prevented the head of the baby from blocking the opening. The duct on the inner face of the plate (Fig. 2 and Fig. 3) is described later (page 54). Padding was placed on the inner surface of the endplate to protect the infant's head from the sharp edges of the duct and baffle.

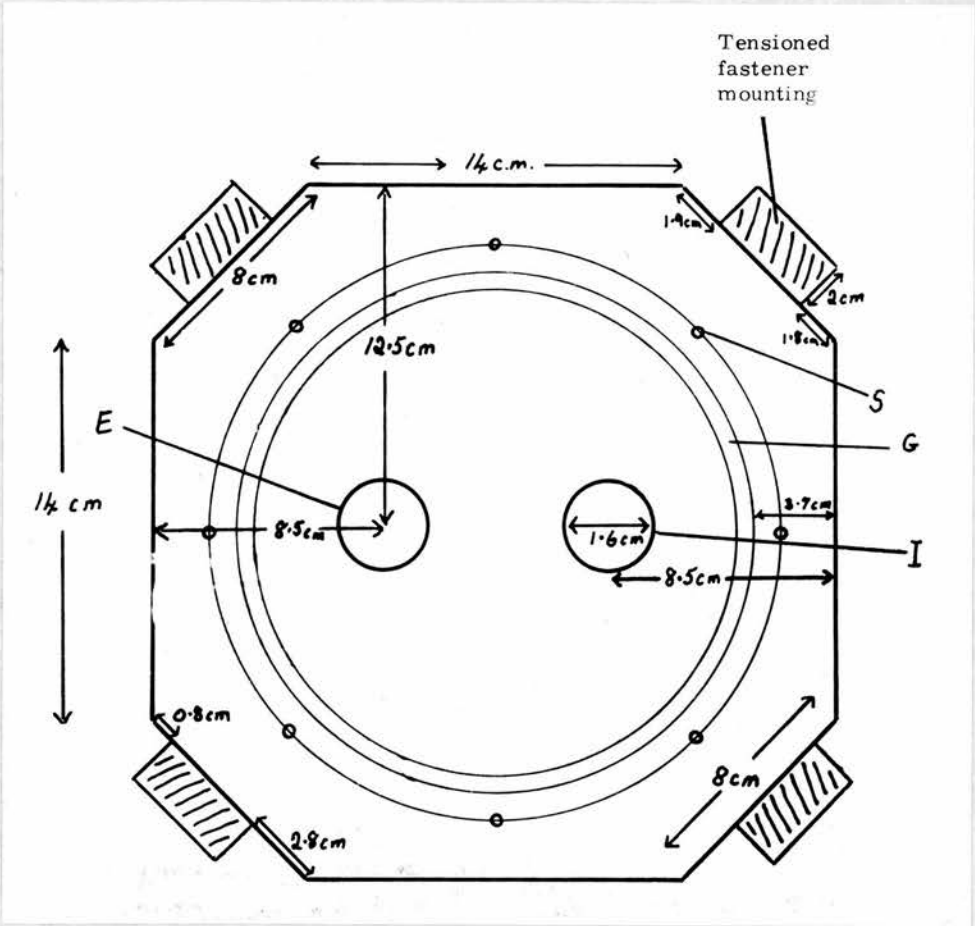


Fig. 4. METABOLIC CHAMBER: Fixed end plate, outer aspect.

The site of the tensioned fastener mounting is shown and S indicates the position of the holes for the guiding screws from the vertical supporting slabs. G indicates the site to which the gasket was applied. The openings I for the gas to enter the chamber from the thermocouple system, and E for the gas to leave it are shown.

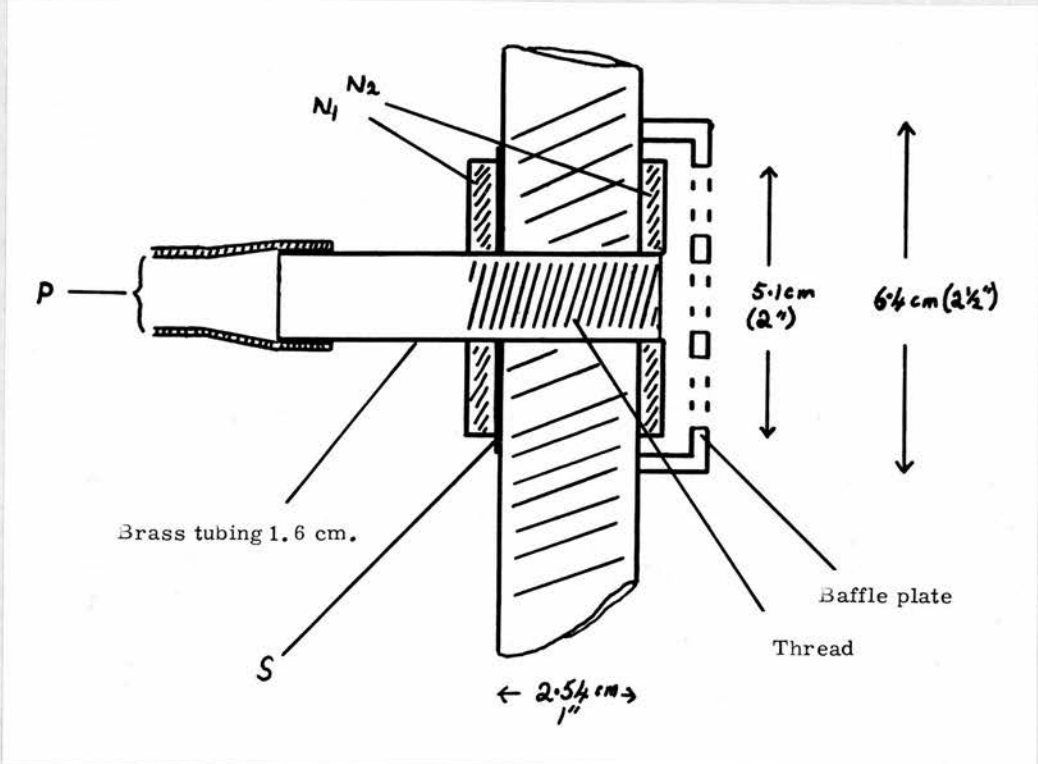


Fig. 5. METABOLIC CHAMBER: Fixed end plate, vertical section through opening for ingoing gas.

N_1 was a 2" diameter, $\frac{3}{8}$" thick, hexagonal brass nut screwed to the limit of the thread with sealing compound S between it and the perspex plate. N_2 was a similar nut. P was 1.3 cm. ($\frac{1}{2}$") bore polythene tubing, which led gas from the thermocouples and the preheater.

Apparatus (cont'd).

Vertical Supporting Slabs.

Both ends of the two cylinders which comprised the metabolic chamber and the water-jacket were mounted on vertically arranged 1.9 cm. ($\frac{3}{4}$") thick slabs of perspex which bore the whole weight of this part of the apparatus. The slab nearest to the entrance plate seen from the metabolic chamber side is shown in Fig. 6. The base was horizontal and rested directly on a chipboard shelf which supported the whole structure. Both slabs contained two accurately cut concentric circular grooves into which the ends of the metabolic chamber and the water-jacket cylinders were inserted and secured by perspex cement; the perspex between these two grooves was bathed in water. The large circular central opening gave access to the metabolic chamber. It was about 2 cm. ($\frac{3}{4}$") narrower than the inside of the chamber, so that if an infant could be inserted through the opening more room was available inside. This factor was of some importance with larger babies. The edges of the opening were carefully rounded.

The outer aspect of the vertical supporting slab is shown in Fig. 7. The circle marked S on the diagram passes through the position of the centres of the guiding screws which were 8.3 cm. ($3\frac{1}{4}$") screws threaded through the slab from the water-jacket side through accurately drilled holes. They projected about 3.5 cm. ($1\frac{1}{4}$") from the outer surface. The screw heads were protected from the water by perspex covering and perspex cement. The screws passed through holes in the end plate to ensure that it was always put on in the same way and that the hooks and catches of the tensioned fasteners were correctly matched. Originally the end

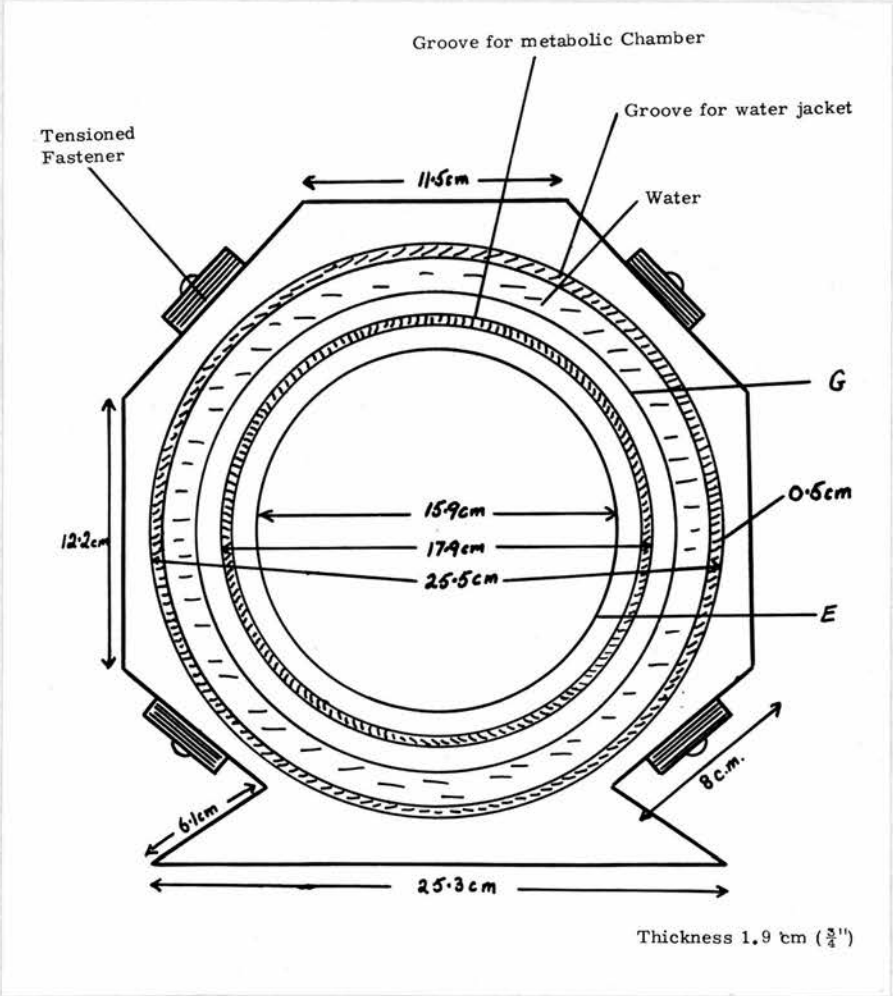


Fig. 6. METABOLIC CHAMBER: Vertical supporting slab, inner side.

The grooves (0.5 cm. wide) for the metabolic chamber and for the water-jacket are shown. Between these two grooves the perspex was bathed by water from the water bath.
G indicates the position where the gasket was embedded, on the outer side of the slab.
Part of the brass mounting for the hooks of the 4 tensioned fasteners is also shown.
E indicates the edge of the circular opening leading on to the metabolic chamber.

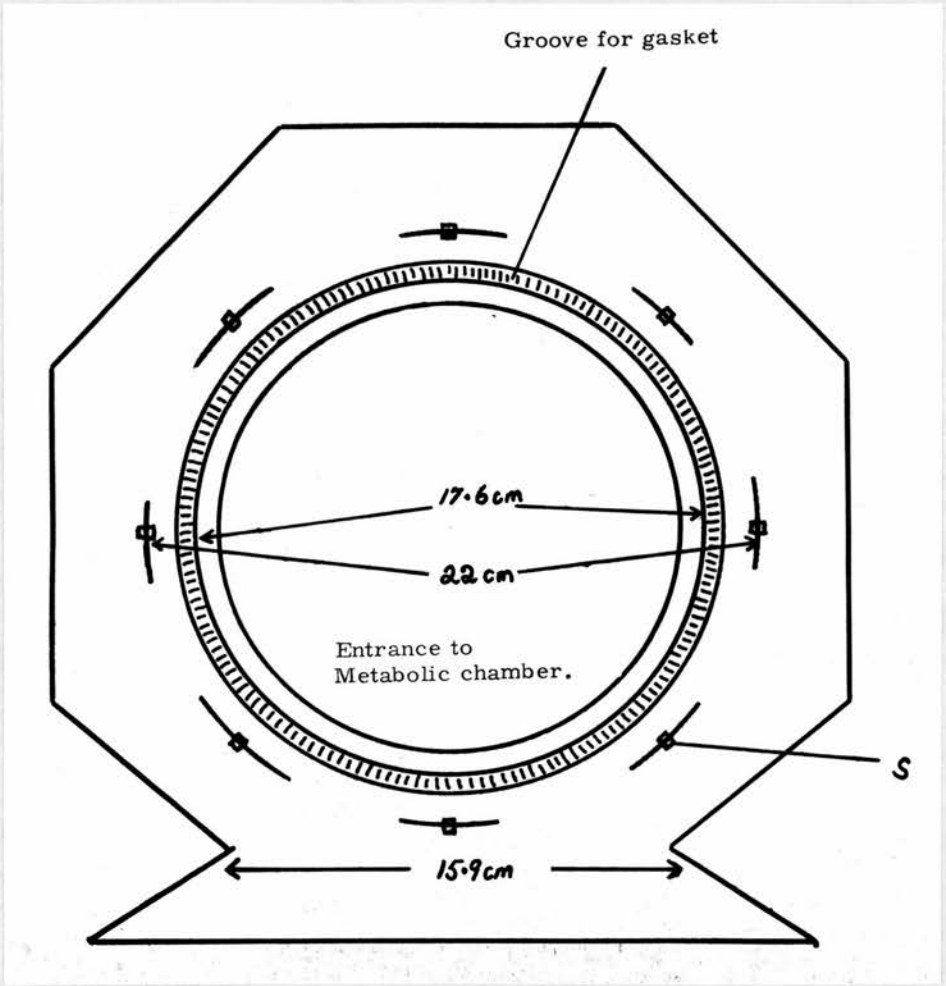


Fig. 7. METABOLIC CHAMBER: Vertical supporting slab, outer side.

The position of the 0.7 cm. wide groove which contains the hard rubber O ring gasket is shown; S indicates one of the projecting guide screws. The entrance to the metabolic chamber is 15.9 cms. in diameter. The tensioned fasteners are not represented.

Apparatus (cont'd).

plate was fixed to the vertical slab by wing nuts screwed on the guiding screws, but the tensioned fasteners were substituted to give more rapid access to the infant in an emergency. A small strip of perspex of similar thickness was added to the original slab to widen the base and promote stability: for clarity this has been omitted from the diagram.

In Fig. 7 the grooves for the water-jacket and metabolic chamber have been omitted although they would normally show through the perspex. Fig. 7 shows the groove, 0.7 cm. wide and about 0.5 cm. (3/16th") deep, which contained the gasket, a hard rubber O-ring which projected about 0.3 cm. (1/8th") proud from the slab when the end plate was not in position. The vertical supporting slab near the fixed end of the chamber was similar to that at the entrance end.

The Tensioned Fasteners.

Four tensioned fasteners secured each end plate to the corresponding vertical slab. Their positions are indicated in Figs. 2, 4, and 6. Fig. 8 is a sketch of the mechanism. The lever handle about 4 cm. long was shaped to fit the fingers and pivoted at one end on its base. The catch was a piece of metal shaped like an elongated capital U. The extremities of both the upright limbs were pivoted on the handle 0.5 cm. from its attached end while the base of the U slipped onto a hook mounted on the vertical slab. The catch pulled the hook and handle together.

With a relatively small pressure on the lever handle a considerable force could be applied to the catch and hook because a force exerted on the end of the handle was multiplied 8 times by the mechanical

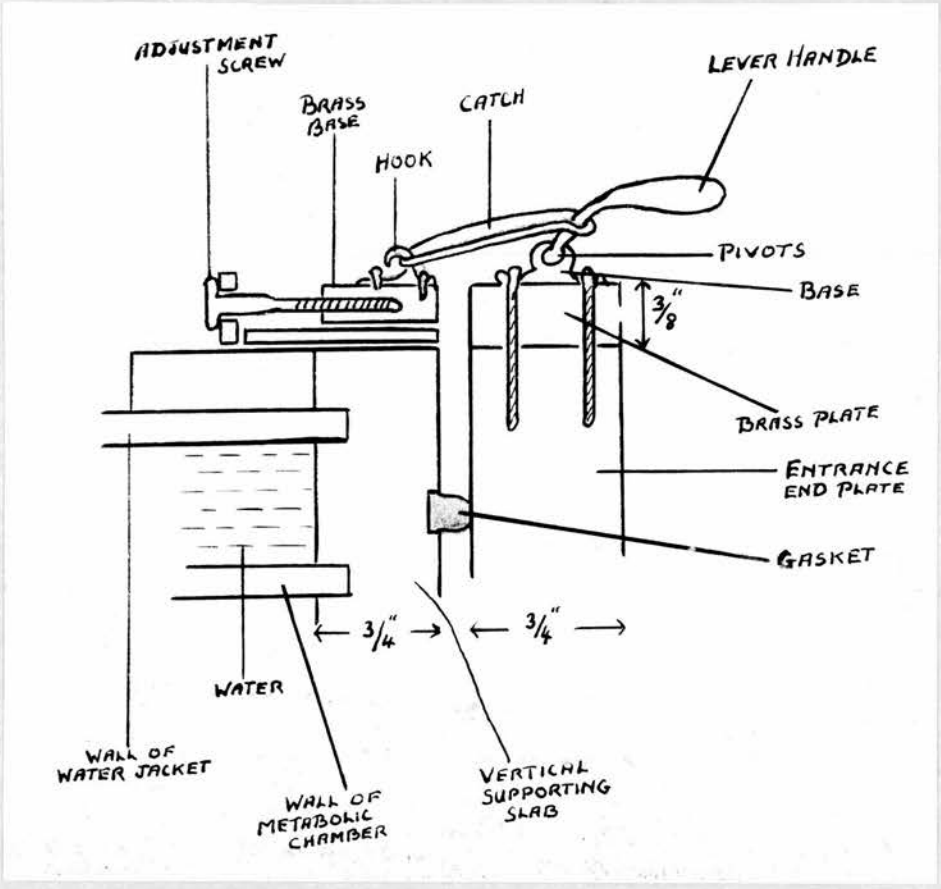


Fig. 8. Tensioned fastener sketch, not to scale. The entrance end plate was separated by the gasket from the vertical supporting slab. The lever handle was pivoted at the base while the catch was pivoted on the lever handle itself. The hook engaged the catch. The hook and handle were mounted on 2 brass plates, which were screwed to the perspex. A screw in the base of the hook allowed fine adjustment of it. The water-jacket, water, and metabolic chamber are also shown.

Apparatus (cont'd).

advantage. (The mechanical advantage is the ratio:

$$\frac{\text{the distance from end of handle to pivot}}{\text{the distance from pivot of catch to pivot of base.}}$$

) In this way the end plates could be forced against the vertical supporting slabs to compress the rubber O-ring gaskets and ensure a leakproof seal. The tensioned fasteners were quick and simple to operate and this was perhaps the most satisfactory method of obtaining a leakproof seal. They were also quick and simple to release. Each fastener could be released in less than a second to allow access to the infant.

Details of mounting. The lever handle, brass base and catch of each of the fasteners were mounted on a brass base 1 cm. ($\frac{3}{8}$") thick, 4 cm. long ($1\frac{5}{8}$") and 1.9 cm. ($\frac{3}{4}$") wide. Two 3 cm. ($1\frac{1}{4}$") brass screws secured the base of the fastener and the brass base (Fig. 8) to the perspex.

The hook was screwed into a brass base mounted in a channel in a brass plate which was secured to the vertical supporting slab (Figs. 8 and 9). The brass plate was screwed to the vertical supporting slab and to an underlying block of perspex 2" by 2" by $\frac{1}{2}$" deep. The perspex block was shaped to fit the outer wall of the water-jacket and was screwed and cemented to it and the vertical supporting slab.

It was important to provide fine adjustment for the siting of the hooks so that equal tension could be exerted on each. Adjustment was provided by a screw which passed through a plain hole in the brass plate and was then screwed into the brass base of the hook (Fig. 9). Turning the screw caused backward and

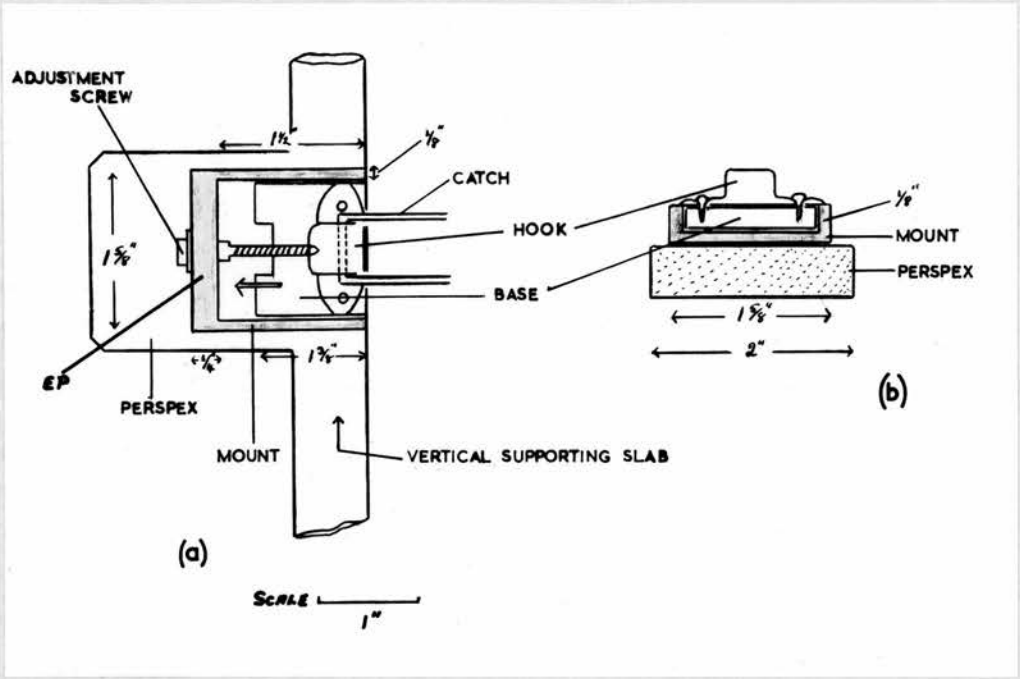


Fig. 9. Mounting of tensioned fastener hook.

Diagram (a) is a plan view of the hook screwed to a brass base. In diagram (b) the hook, brass base, and perspex are shown in cross section. The base fitted exactly into the channel in the mount which was a single piece of brass with the dimensions indicated. The spaces between the base and the mount are exaggerated to bring out the point that they are separate. The base was made to slide in the groove in the mount. The position of the base was controlled by the adjustment screw, which passed through a smooth hole in the brass plate at the end of the mount (EP) and was screwed into the base. When the screw was turned the base moved in the direction of the arrow and more tension was put on the catch. A gap was cut into the base to accommodate the screw when the hook was adjusted to be as tight as possible. The screw was normally covered by a brass lid. The brass mount was screwed to the underlying perspex and to the vertical supporting slab. All the original measurements in this diagram were made in inches and to avoid excessive detail centimeter equivalents have been omitted.

Apparatus (cont'd).

forward movement of the hook on its base so as to alter the tension on the catch. The adjustment mechanism was concealed by a thin brass cover.

Dimensions of Chamber.

The chamber was basically a carefully moulded open ended cylinder made of 0.6 cm. ($\frac{1}{4}$") thick perspex with an inside diameter of 16.9 cm. ($6\frac{3}{4}$") and length 44.5 cm. ($17\frac{1}{2}$") supported at both ends which were securely cemented into the vertical supporting slabs.

The dimensions of the chamber were specifically selected for satisfactory examination of the normal full term infant; the length of the cylinder (about $17\frac{3}{4}$") approximated sufficiently closely to the average length of the normal infant at term (20"). The internal diameter 16.9 cm. ($6\frac{3}{4}$") gave ample room for the greatest diameter of the head (in the occipito-frontal plane) which is of the order of 5". The baby normally lay with his head towards the fixed end plate and feet towards the entrance end plate. When a baby was being put in the chamber he was placed on a specially shaped tray which was then slid inside. The chamber also contained the rectal thermo-couple leads and a system for ducting the incoming and outgoing circuit gas. The volume available in the chamber was 10.0 litres when empty, and about 6.6 litres with a baby inside.

Circulation of Gas.

It was found more convenient to lead the gas into and out of the chamber through a single end plate than to have gas entering at one end of the chamber and leaving at the other. This allowed one end plate to be much more easily removed and replaced because it was unencumbered by plastic tubing connecting gas to the rest of the closed circuit. As the fixed end plate was

Apparatus (cont'd).

rarely removed the presence of both the entrance and exit tubing there was of little consequence. This arrangement also permitted the relatively delicate glassware which contained the thermo-couples measuring the temperatures of the in and outgoing gas to be concentrated in one place. However to ensure an adequate circulation within the chamber and to prevent rebreathing gas had to be made to enter one end of the chamber and leave at the other.

Gas entered the chamber through the aperture and baffle plate in the fixed end plate, travelled past the infant's head towards the feet and then into a channel attached to the upper part of the chamber. The channel began about 5 cm. (2") from the entrance end plate and conducted gas to the opposite end of the chamber. It was made of 0.5 cm. ($\frac{1}{8}$") thick perspex and was roughly C shaped in cross section; the open part of the C was closed by the sides of the channel which were cemented to the upper part of the chamber (Figs. 2 and 10). In the channel gas flowed from the entrance end of the metabolic chamber to the closed end i.e. in the opposite direction to the gas in the rest of the chamber. A small perspex tube directed the gas out from the channel to the duct in Figs. 2 and 3. The duct was rectangular in cross section and was also formed from 0.3 cm. thick perspex. It was cemented to the inner side of the attached end plate and projected about 1.3 cm. ($\frac{1}{2}$") from it. The duct ended over the aperture in the fixed end plate for the outoing gas. The dimensions of the metabolic chamber and its relation to the water jacket and vertical slabs are indicated in Figs. 2 and 10.

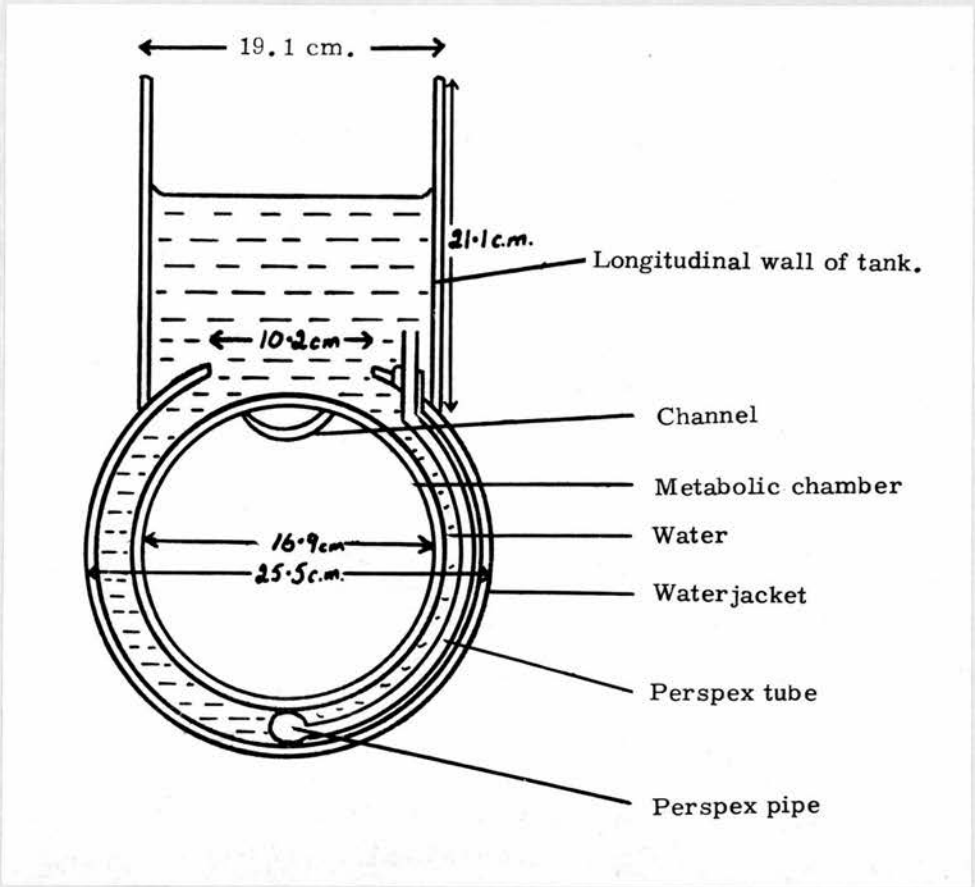


Fig. 10. METABOLIC CHAMBER: Transverse section through metabolic chamber, water-jacket, and tank.

The longitudinal wall of the tank was made of 0.6 cm. ($\frac{1}{4}$") thick perspex and the communication between the water-jacket and the tank is shown. The channel for the outgoing air was at the top of the metabolic chamber. The perspex tubing conducted water from the tank to the perspex pipe running along the bottom of the water-jacket.

Apparatus (cont'd).

The Water-Jacket.

The water-jacket entirely surrounded the sides of the metabolic chamber and like it consisted basically of an open ended cylinder of 0.6 cm. (¼") thick perspex of exactly the same length as the chamber but with an inside diameter of 24.2 cm. (9½"). Both ends were cemented in to the vertical supporting slabs. Between the outer wall of the metabolic chamber and the inner wall of the water-jacket was a distance of 3.3 cm. (1⅜") which was filled by freely circulating water. Water was pumped round the water-jacket, tank and heat exchanger, (see page 58). The perspex wall of the metabolic chamber was in thermal equilibrium with the water of the water bath and the outer wall of the water-jacket was in contact with room air (Figs. 2 and 10).

In the upper part of the water-jacket was a round opening 10.2 cm. (4.0") diameter which allowed water to pass freely from the water-jacket to an overlying tank, (see Figs. 2 and 10). The tank was necessary to contain the equipment needed for circulating the water and maintaining it at the desired temperature. It consisted of four upright sides of 0.6 cm. (¼") thick perspex cemented on the outer wall of the water-jacket. The two walls arranged parallel to the long axis of the metabolic chamber were cemented to the curved sides of the water-jacket by their lower edges which were specially shaped. The two transverse walls were shaped to have the same radius of curvature as the outer wall of the jacket and were screwed and cemented to it.

Fig. 2 shows the chamber, the water-jacket and tank sectioned down their long axes. Fig. 10 is a transverse

Apparatus (cont'd).

section through the middle of the metabolic chamber, water-jacket and tank.

Temperature Control and Circulation of Water.

Temperature regulation.

The temperature of the water and its circulation round the water-jacket and the preheater were controlled from the tank. The tank contained the following equipment for circulating the water and maintaining the desired temperature:-

1. Circotherm constant temperature unit, including pump.
2. Thermocouple.
3. National Physical Laboratory calibrated thermometer (0-45°C in 0.1°C divisions).
4. Two coil heaters, each a thousand watts.
5. Connections leading water from the Circotherm pump.
   a. To the preheater
   b. To the perspex tube and pipe in the water-jacket.

The Circotherm Constant Temperature Unit. This unit is available commercially (Shandon Scientific Company, London, Model No. 968). It comprises very briefly:

A. A pump capable of discharging a maximum of 7 litres per minute.

B. A 700 watt heater, with a red light which indicates when the heater is on.

C. A contact thermometer which controls the heater by switching it off when the water bath temperature rises and switching it on when the water bath temperature falls.

Apparatus (cont'd).

D. A reference thermometer on which the water bath temperature can be read accurately (0-50°C in 0.2°C divisions) provided with Circotherm.

The thermocouple. The water bath temperature was measured by a thermocouple which was encased in a J shaped piece of glass tubing so that the tip of the thermocouple was just inside the opening between the water-jacket and the tank. The thermocouple was connected to the six channel recorder (see later) and its reading was recorded every 36 seconds. As a further check the National Physical Laboratory calibrated mercury thermometer was placed in the tank and read at 10 minute intervals. The stem of this thermometer was passed through a small hole in the water-jacket and its bulb was placed between the water-jacket and the metabolic chamber.

The circotherm maintained a given water-bath temperature to within ± 0.05°C without further attention, with one exception, (see below). It could be readily reset at a higher or lower temperature and it was possible to stabilise the water at a temperature 2 or 3°C different from the original within about 3 minutes. When raising the temperature the extra heaters could be used for a time to supplement the circotherm heater. When both heaters were switched on for about 15 seconds the water temperature rose by about 1°C. To lower the temperature more quickly ice was added.

When the water bath temperature was near that of the room it tended to drift upwards if precautions were not taken because of the unavoidable heat gain from the baby, the room and the Cirotherm pump. To avoid this situation

Apparatus (cont'd).

at water bath temperatures near or below room temperature, ice was continuously added to the water so that the temperature tended to drift downwards, a tendency which was easily corrected by the heater.

Circulation of Water.

From the outlet of the circotherm pump 1.3 cm. (½") bore polythene tubing was connected to the upright limb of a T junction. One horizontal limb played a part in circulating the water inside the water-jacket, while the other directed water to the preheater (see below). The first limb led to a perspex tube (see Fig. 10) which was mounted on the water-jacket in the floor of the tank. The tube conducted water round the metabolic chamber to the lowest part of the water-jacket. Here it was moulded to join the centre of a 43 cm. (17") length of perspex piping (Figs. 2 and 10) which ran along the bottom of the water-jacket. Both ends were closed but from side holes 0.5 cm. (3/16") diameter at intervals of 2.8 cm. (1½") the water escaped into the rest of the water-jacket. The water then rose to reach the tank and pump at the top of the water-jacket and a thorough circulation of water was ensured.

The preheater.

Part of the outflow from the cirotherm pump was directed from the horizontal limb of the T piece mentioned above, along polythene tubing to the glass preheater. The preheater shown diagrammatically in Fig. 1 was a commercially available jacketed coil condenser, surface area 550 sq. cm. (Griffin and George Limited, Cat. No. C11/23). Its relation to the rest of the apparatus is shown in Fig. 1. Although it was

Apparatus (cont'd).

primarily intended for condensing volatile liquids, its large surface area was equally effective in warming the incoming air to almost the same temperature as the water bath.

Water was circulated through the condenser at about 2 litres per minute. The total volume of water in the preheater, water-jacket, tank and connections was about 12.5 litres.

The circuit gas entered the lower part of the preheater through a socket (Quickfit size 19/26) into which was fitted a cone connection from the flow-meter; it then passed between the jacket and coil of the condenser and out through a cone (Quickfit size 24/29) to the glass tubing protecting the thermocouples.

Thermocouples measuring dry and wet bulb depression temperatures.

Wet and dry chromel/constanton thermocouples were used to record the temperatures of the circulating gas immediately before it entered, and immediately after it left the metabolic chamber. Chromel rather than copper was used with constanton because of the higher sensitivity and lower thermal conductivity. The thermocouples were placed in protective glass tubing which was specially blown for the apparatus (Aimer Ltd.). For convenience the arrangements for measuring the temperatures of the incoming gas, shown in Fig. 11, are described first.

Incoming gas temperatures.

The gas left the preheater to enter the thermocouple system. It was first passed through a short piece of glass tubing which then divided into:-

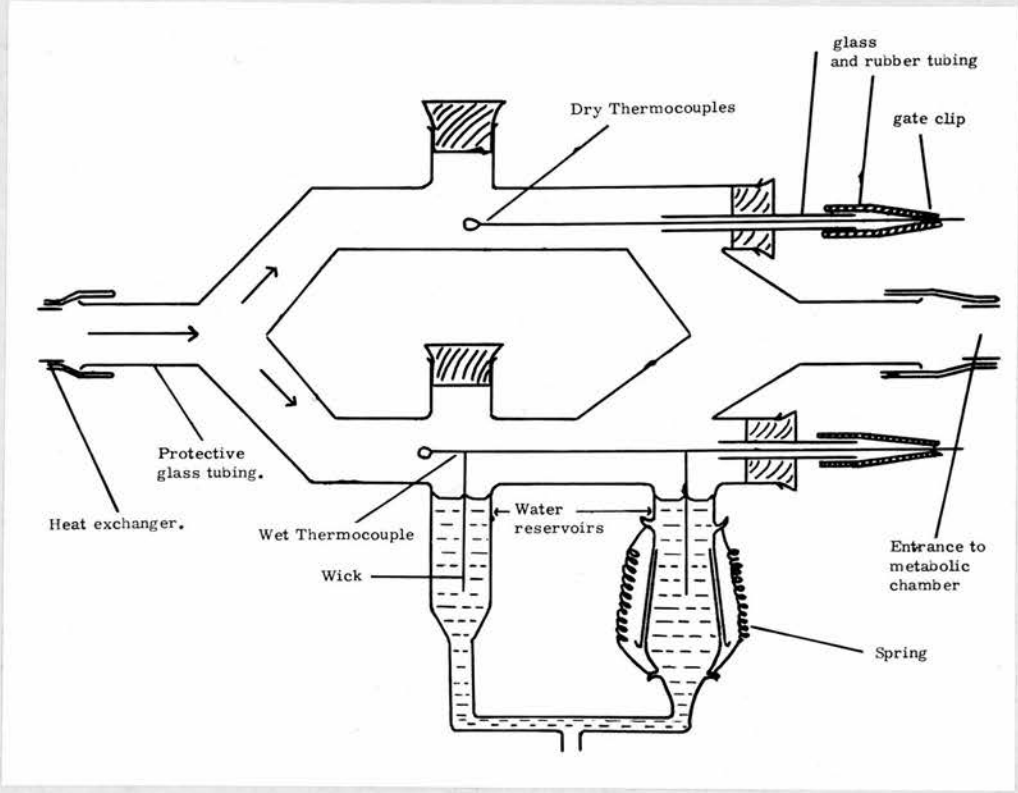


Fig. 11. Protective glass tubing and wet and dry thermocouples for ingoing gas.

The gas entered the tubing from the preheater (called heat exchanger in the diagram), passed through the tubing, and entered the metabolic chamber.

Apparatus (cont'd).

Incoming gas temperatures (cont'd).

1. An upper division, length 7 cm., bore 1.3 cm., which contained two dry thermocouples.
2. A lower division of the same dimensions which contained the wet thermocouple.

The two tubes then joined and the gas passed out through a single tube to enter the metabolic chamber through the fixed end plate, (Fig. 4). The gas was directed through the two narrow tubes to increase its speed which should be greater than about 2 ft./sec. for an accurate measurement from the thermocouple. Assuming a flow rate of 25 litres per minute the gas speed in each of the two 1.25 cm. (½") bore tubes was about 5.40 ft./sec. To record the difference between wet and dry thermocouple temperatures it was necessary to connect the "wet" thermocouple to a "dry" thermocouple, which acted as a reference. For this reason the "dry" tube contained one thermocouple to measure gas temperatures dry and another for comparison with the wet thermocouple. Since the temperature at the tip of a thermocouple may be influenced by the conduction of heat along the wire to or from the room at least 1½" of thermocouple wire was placed inside the protective glass tube, (Notes on Applied Science, 1958).

The Dry Thermocouples. As they passed through the rubber cork fixed in the protective tubing the wires of the thermocouples were shielded by thin glass tubing (length 1 cm.) to keep them away from the sides of the protecting glass. A 1-2"length of soft rubber tubing covered the outer end of the glass tubing. To ensure a leak proof join the rubber was pressed tightly onto the thermocouple cable by two gate clips. The junction end of the

Apparatus (cont'd).
thermocouple lay in the middle of the lumen of the protective tubing immediately beneath a specially designed opening. The opening which normally was sealed by a rubber cork, allowed access to the end of the thermocouple to enable it to be correctly positioned away from the walls.

The Wet Thermocouple. This thermocouple was mounted in a similar arrangement of glass and rubber tubing. It was kept moist by two wicks which extended into the two water reservoirs shown in Fig. 11 and then covered the wiring and thermocouple end. Facilities for making small adjustments to the position of the wiring were necessary and access to the wick in the first water reservoir and the end of the thermocouple could be obtained by removing the overlying rubber cork. The second reservoir consisted of a socket attached to the main part of the apparatus and a fitting cone secured by two springs: the cone was removed to allow access to the wick. Both reservoirs were joined by polythene tubing and connected to a glass T piece, the upright limb of which was attached to a 9" long piece of polythene tubing through which the reservoirs were filled. During the experiment (between observations of oxygen consumption), water could be injected into the tubing to maintain the water level constant without disturbing the rest of the apparatus.

The protective glass and connecting polythene tubing were heavily insulated with 1.3 cm. ($\frac{1}{2}$") thick expanded polystyrene. A small piece of the polystyrene overlying the first reservoir could be removed and replaced so that the water level could be inspected without disturbing the insulation.

Apparatus (cont'd).

Outoing Gas Temperatures.

The wet and dry thermocouples measuring the temperature of the outgoing gas were similarly housed in glass tubing arranged in parallel to that described above.

The gas left the metabolic chamber to enter the thermocouple system and was then conducted along 1.3 cm. (½") bore polythene tubing to connect with the carbon dioxide absorber.

The Carbon Dioxide Absorber.

Carbon dioxide was absorbed by commercially available self-indicating fine mesh soda lime, (Anaesthetic quality Sofnol 5-10 mesh). The soda lime was packed in a vertically mounted perspex cylinder, length 5½", internal diameter 2", and lay on a disc of fine wire mesh. Both ends of the cylinder were enclosed by rubber bungs; the circuit gas entered through glass tubing piercing the lower bung and left through the upper bung.

It was important to prevent a build up of carbon dioxide in the circuit which would tend to keep the volume high and give falsely low measurements of oxygen consumption. To test for the presence of carbon dioxide a sample of the circuit gas which had passed through the carbon dioxide absorber could be bubbled through baryta water; insoluble barium carbonate precipitates out if carbon dioxide is present. Repeated tests over several hours gave negative results.

The Cooling Condensers.

After leaving the carbon dioxide absorber the gas entered the cooling condenser system. The condensers were incorporated into the circuit in order to remove the

Apparatus (cont'd).

water vapour from the expired air, perspiration and occasionally from the urine and faeces. This would otherwise have caused a continuous increase in the humidity and lowering of the percentage of oxygen, which would have invalidated the oxygen consumption measurements.

If the humidity had been permitted to increase part of the fall in circuit volume which should follow removal of oxygen from the circuit would have been taken up by water vapour and the concentration of oxygen would have gradually fallen. If this had occurred the volume of oxygen added to the circuit would have underestimated the amount of oxygen used.

The condenser was perfused with water at a constant temperature to ensure that the air leaving the condenser was fully saturated and to maintain the vapour pressure constant. The actual relative humidity can be obtained from tables if the gas temperature is known. One other requirement of the condenser temperature was that it should be high enough to ensure that the humidity was not unduly low.

A condenser temperature of 10°C was selected and at this temperature there was a steady drip of water indicating that the air was fully saturated. The humidity is further discussed in the section on thermal environment.

Details of Condensers. Polythene tubing 1.3 cm. (½") bore connected the carbon dioxide absorber to an adaptor 11 cm. long (C8B19, see below), with projecting hooks which allowed it to be more firmly secured to the underlying condensers. Two condensers (CX6/22) were arranged in series vertically (surface area of each

Apparatus (cont'd).

430 sq. cm.) and perfused in parallel by water at 10°C. These condensers were of the jacketed coil type in which the cooling fluid in the central coil passes into the jacket before leaving the condenser. The lower condenser was connected to an adaptor one arm of which transmitted the gas to the rest of the circuit, while the other was fitted into a small 25 ml. flask which collected the water. Both condensers were heavily insulated with 1.9 cm. ($\frac{3}{4}$") layer of glass wool.

All of the condenser system is commercially available from Quickfit and Quartz Ltd., Stone, Staffs., England. The bracketed numbers after the preceeding items are the numbers in the catalogue.

Circulation of Water through the Condensers. The condensers require a flow of water at a constant temperature lower than that of the room, and to provide this, water cooled from melting ice was warmed to a constant temperature.

Water at approximately 1°C. A 10 litre thermos flask in a wooden case was packed with ice and water at the beginning of the experiment. Water was drawn from the bottom of the flask by a pump (model C16/300 Charles Austen Pump Ltd., Byfleet, Surrey, England) which was supplied at 110 volts by a Variac resistance. The water was circulated round a cooling coil and returned to a vacuum flask.

Water at 10°C. The coil was used to cool the water of a second vacuum flask which also contained a thermostatically controlled heater (Circotherm, Shandon Scientific Co., Model No. 968). The heater warmed the water to a constant temperature of 10°C.

Apparatus (cont'd).

Water was pumped from the second flask past a thermometer through the condensers and back to the flask again. A centrifugal pump (Stuart and Turner, Henley, England, Type No. 10) was used to draw water through the condensers. It was capable of an output of 120 gallons per hour and was used in preference to the much less powerful pump on the Circotherm. The thermometer in this circuit was read every 10 minutes and did not vary from 10°C.

After leaving the condensers the gas passed along 1.3 cm. (½") bore polythene tubing, through a horizontally mounted piece of glass tubing with six side arms. The side arms were connected to the circuit float, the oxygen meter unit and a syringe for withdrawing gas from the circuit. Three lengths of occasionally used polythene tubing were also connected. The gas next passed to the pump.

Pump to Circulate Circuit Gas.

The proper function of the apparatus, which relied on the interpretation of small decreases in volume as removal of oxygen from a closed circuit, was very dependent on the correct choice of pump.

Hill,(1959) in her description of a similar apparatus used for animals mentioned the criteria the pump must fulfil. Clearly it must be absolutely leak tight or mounted in a leak tight housing; the output must be free from the rapid changes of roller, piston and diaphragm driven pumps which would tend to set up vibrations in the circuit float and distort the oxygen consumption record. Also the output must be free from slower minute by minute changes which tend to give a falsely high or low oxygen consumption while the pump is accelerating or decelerating. It must be sufficiently

Apparatus (cont'd).
powerful to overcome the circuit resistance, which amounted to a few centimetres of water, while maintaining a gas flow which is high enough to prevent any possibility of rebreathing.

Rate of Flow of Gas. It is difficult to know exactly what gas flow is needed to prevent rebreathing but this is a point which has been closely considered in the design of open circuit apparatus where it is particularly important. In open circuits the volume of gas diluting the expired air must be kept as low as possible so as not to diminish the already small difference between the percentage of oxygen in the gas approaching the subject and that leaving it.

On the other hand if there is too low a flow there is a danger of rebreathing and a balance must be struck between these two opposing factors.

Cross, Tizard and Trythall (1957) measuring the oxygen consumption of newborn infants in an open circuit and using a close fitting face mask found there was no accumulation of carbon dioxide with a flow rate of 2 litres per minute. Oliver and Karlberg using an open circuit and a plastic hood over the face and head employed a flow rate of 4.6 litres per minute, 10 times the predicted minute volume. The actual velocity of the gas is also important in assessing the liability to rebreathing. Adamsons et al. (1965) used a pump with a maximum flow rate of 45 litres per minute and at 25 litres per minute the gas speed was less than 5 cm. per second. In the present apparatus the gas speed with the baby in situ was of the order of 3 cm. per second and the flow rate was 25 litres per minute.

Apparatus (cont'd).

Details of Pump and Mounting.

A pump removed from a Hoover Dustette was found to be suitable. It was sufficiently powerful to maintain an output of 25 litres per minute in spite of the circuit resistance. It was under run, at below maximum output from a supply of 90 volts via a Variac resistance. Repeated tests showed that the position of the circuit float was constant when the pump was in use and there was no baby in the circuit.

The pump was contained in a brass cylinder with both ends closed by identical aluminium cones which tapered to 1.6 cm. ($\frac{5}{8}$") outside diameter piping over which the polythene tubing was placed. The cones were separated from the cylinder by O ring gaskets and secured to it by wing nuts. The difficulty of providing a leak proof seal for the electric cable was overcome by passing the cable through a 1.3 cm. ($\frac{1}{2}$") diameter bore pipe soldered to the side of the cylinder. A piece of soft rubber tubing was fixed tightly over the end of the pipe by a jubilee clip and over the cable itself by wire.

The Rotameter.

Immediately after leaving the pump the gas entered the rotameter, (commercially available from Rotameter Manufacturing Company, Croydon, Surrey; 0-40 litres per minute in 1 litre steps). After leaving the rotameter the gas entered the preheater. The rate of gas flow was 20-25 litres per minute.

Thermal Environment.

Heat exchange between the infant and the environment depended on the four factors of conduction, convection, evaporation and radiation; a complete discussion of the

Apparatus (cont'd).

thermal environment involves indicating the role of each of them. However a quantitative assessment of these factors is not strictly relevant. Provided the thermal environment remains constant when it ought, we are concerned only with the net effect and whether the oxygen consumption is or is not at its minimum.

The water bath temperature, which was almost the same as that of the preheater, was the most important factor in the heat exchange and all the factors mentioned above, except for evaporation, were directly dependent on it.

The gas entering the metabolic chamber was warmed by the preheater to almost the same temperature as the water bath. Because the water cooled slightly en route to the preheater the temperature of the entering gas was always slightly less than that of the water bath. The difference narrowed as the water bath temperature was lowered. Fig. 12 shows the relation between chamber (box) air temperatures measured by a thermocouple in the box, to water bath temperatures. At the maximum temperatures used in the experiments here described, about 35°C, the maximum difference was less than about 2°C.

The infant, who was usually naked except for a nappie, lay on a plastic tray which was in direct contact with the inner wall of the metabolic chamber. The greater part of the dorsal surface of the infant was therefore conducting heat to the tray at a rate which was proportional to the temperature difference between baby and the water bath. Many of the subjects of the later experiments were clothed and in these this form of heat loss was lessened.

Apparatus (cont'd).

The speed of the gas and its temperature influenced the loss by convection and high speeds have an important effect on convective heat loss. In the apparatus the gas speed was maximum around the head and here it was about 3 cm. per second (5 ft. per minute). Near the trunk and the feet the gas speed was slower still. Reference to the tables of the effect of the wind speed (Bedford, 1940) shows that wind speeds of this order have an insignificant effect on heat loss and that this speed is not significantly different from still air.

Evaporative heat loss in the subjects described, who were usually in a cool environment, was primarily from insensible perspiration and the respiratory tract. Urine collecting bags were attached so that the baby was not subjected to extra cooling from evaporation of urine from the skin. The evaporative heat loss is dependent on the humidity of the atmosphere. In the apparatus the water vapour pressure was constant at 12.3 millibars which is the water vapour pressure in air at 10°C when it is fully saturated; 10°C was the temperature of the condenser. This provided an acceptable relative humidity at the range of temperatures used, (17% at 40°C to 53% at 20°C.) The estimates of relative humidity derived from the thermocouples agreed well with those derived from tables of relative humidity for a water vapour pressure of 12 millibars.

The recent work of L. E. Mount (1964) has sharpened interest on the heat losses by radiation. Mount calculated that 50 to 59% of the heat loss from the skin of the newborn pig was by radiation and commented that

Apparatus (cont'd).

his estimate agreed well with that of Burton and Edholm (1955) for man. Mount showed that if the temperatures of the radiant surfaces and the air around the pig were varied independently there were marked changes in oxygen consumption. Lowering the wall temperature (to which the pig was radiating) by 10°C when air temperature was held constant increased the oxygen consumption by 40%.

In our apparatus the baby radiated to the surrounding perspex wall and the water of the water bath; as water is virtually opaque to radiation we are not concerned with the problem of radiation through it. The water bath and the inner perspex wall were at approximately the same temperature as the circulating gas. Mean wall temperatures obtained after equilibration are shown in Fig. 12. At 35°C the wall temperature was only 2°C less than the water bath temperature, and at lower temperatures the difference was even less. The radiant temperature (temperature of the surface to which the infant is radiating) was very closely defined in this apparatus as lying between the water bath temperature and that of the inner perspex wall. (The exact radiant temperature must depend on factors such as the transmission of radiation of different wave lengths by the perspex and the wave lengths of the radiation emitted by the baby.)

All the above factors and also the posture of the infant influence heat loss and heat production and it is obviously unlikely that their net effect can be expressed by any single value.

The relative humidity and the wind speed have been defined and the important remaining factors are gas temperature and the radiant temperature of surrounding surfaces.

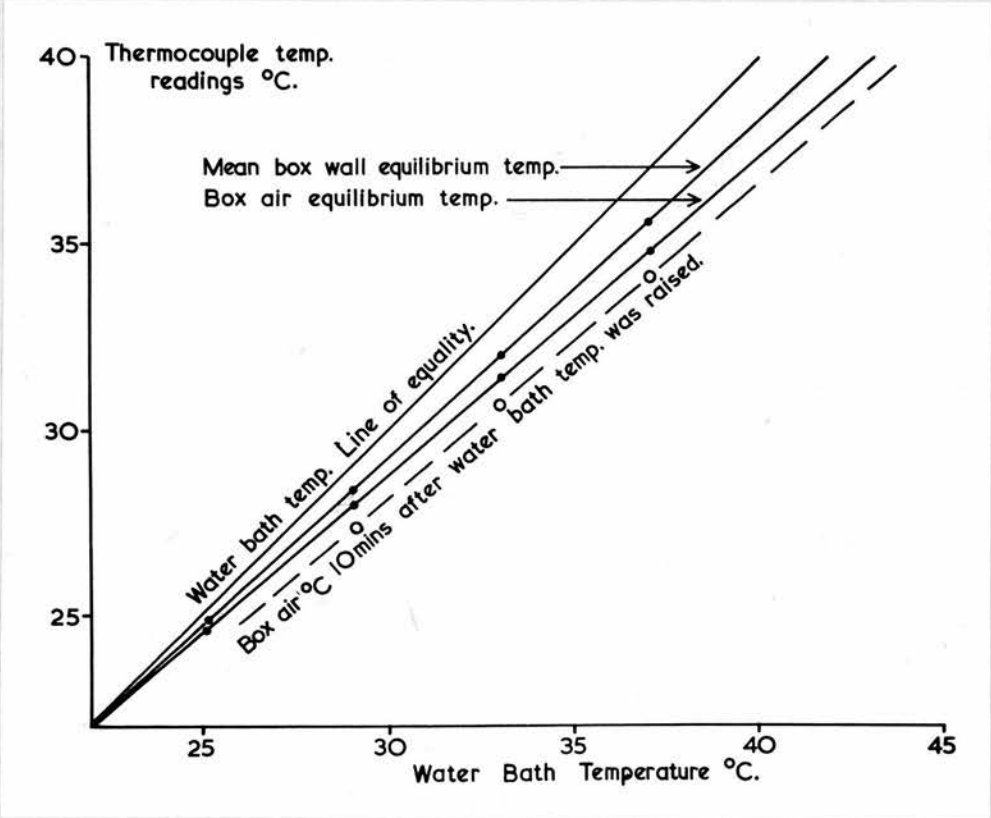


Fig. 12. Water bath and metabolic chamber (box) air and wall temperatures.

Thermocouple temp. readings °C indicate the temperatures recorded by thermocouples fixed onto the perspex wall of the metabolic chamber, and hanging freely in the air of the chamber.

The equilibrium temperatures were reached after 20 minutes.

Apparatus (cont'd).

As shown above the gas and radiant temperatures are a little different, and as a considerable portion of the heat lost is by the 2 channels of convection and radiation the question arises as to whether the small difference in the temperatures is important, and which ought to be regarded as the environmental temperature.

Yaglou (1949) stated that in many laboratory tests the need for measuring radiation intensity may be obviated by keeping all room temperatures at approximately air temperature.

Similarly Mount while investigating the effect of changing the wall and air temperatures, disregarded air-wall temperature differences of less than 1°C. Adamsons, Gandy and James (1965) stated that when the temperature of the gas and the radiant surfaces are nearly identical either can be used as a measure of environmental temperature. When they are different neither can serve as an index of "environmental temperature" and the term should not be used. They used the term as did Scopes (1966) when the ambient air and radiant surface temperatures were similar and the difference was less than $\pm$ 2°C.

It would seem that for practical purposes one can disregard a difference between radiant and gas temperatures of about 2°C or less and in this apparatus the gas wall temperature differences are well within these limits. For practical purposes some single easily measurable value which will be reasonably representative must be selected. The water bath temperature was chosen as being the most suitable. It was recognised that as it was the warmest part in the whole system its temperature may well have been slightly higher than any of the individual factors considered.

Apparatus (cont'd).

The Oxygen Meter.

To achieve known changes in oxygen concentration quickly and safely it was important to have a method of estimating oxygen concentration which was rapid and precise. Apart from the convenience of having a continuously available reading of the oxygen concentration, once the oxygen concentration had been lowered safety dictated that it be continually measured to avoid dangerously low levels. A Cambridge oxygen measuring unit (paramagnetic type Instrument No. C660596) was connected to a side arm from the circuit and part of the circuit gas continually pumped through it by a small aquarium pump, via a tube of silica gel. The silica gel was packed in a vertically arranged 1" internal diameter glass cylinder; the gas entered the lower part of the cylinder and left at the top. The indicator in the silica gel demonstrated the presence of water by turning from blue to pink; the silica gel protected the oxygen meter from moisture and incidentally indicated the efficiency of the condenser in removing water vapour from the circuit gas. It eliminated the possibility of a high moisture content in the gas examined causing a low reading for percentage of oxygen, and artefacts due to condensation within the meter. Even after a long experiment (3 hrs.) the lower part showed only a slight trace of pink.

Standardisation.

Every day on which an experiment was performed the oxygen meter was zeroed and then standardized by passing through it low oxygen mixtures at 2 litres a minute for 5 minutes (5, 10 or 15% oxygen in nitrogen from cylinders were used). At the end of this time the meter was read

Apparatus (cont'd).

and the observed values graphed against the concentrations in the cylinders. Wherever possible two low oxygen mixtures were used but it was often difficult to obtain more than one cylinder at a time and it was not thought reasonable to delay experiments for this reason. During the experiments the oxygen meter readings were recorded every 10 minutes and later plotted on the graph; the corrected values were recorded in the experimental results.

Accuracy. Review of the readings obtained when 5, 10 or 15% oxygen and air (20.95% oxygen) were pumped through the meter showed that the value indicated was within 0.5% of the true value, except in 7 cases out of 42. The total range of variation of the readings was 1% in air, and 0.8% in 15% oxygen over the course of a year. When it became apparent that we were unable to reproduce the earlier work of Cross et al. (1958) and Oliver and Karlberg (1963) the oxygen meter was checked to eliminate the very remote possibility that we were giving oxygen in concentrations which were different from 15%. The usual meter was calibrated with a Servomex oxygen meter. Both meters estimated oxygen content of air as 20.95% and agreed to within 0.2% in their estimations of the oxygen content of gas from cylinders of 15% and 5% oxygen.

Cambridge 6 Channel Recorder.

The temperatures of the 6 thermocouples mentioned - the rectal thermocouple, thermocouple measuring water bath temperature, and the 4 thermocouples measuring wet bulb depression and dry bulb temperatures of gas entering and leaving the metabolic chamber - were recorded on the 6 channel recorder. Each temperature was recorded every 36 seconds, and the record appeared as a row of dots.

Apparatus (cont'd).

The accuracy of the thermocouple in the water bath was checked by comparison with the National Physical Laboratory (N.P.L.) calibrated mercury thermometer which was placed in the water near the thermocouple. The rectal thermocouple was checked by placing it in the water bath which was heated to about 37°C and comparing its assessment of the water temperature with that of the N.P.L. calibrated mercury thermometer.

Apparatus (cont'd).

SYSTEM FOR REPLACING AND RECORDING OXYGEN USED.

This system comprised three float recorders, separated by electro-magnetic valves, which were activated by two electrical circuits controlled partly by photoelectric cells. The three float recorders are described in the order of their proximity to the closed circuit.

1). The circuit float was directly connected to the circuit and was maintained at a constant volume by the addition of oxygen which came via a valve from the differentiating float. The rate of inflow of oxygen through the valve was controlled by the action of a photo electric device.

2). The differentiating float emptied into the circuit float and the movements were recorded on a kymograph. It had only a small capacity and was refilled at preset intervals by oxygen from the storage float.

3). The storage float had a large capacity and emptied through a second valve into the differentiating float. It was refilled by hand.

The Circuit Float.

A narrow 0.65 cm. ($\frac{1}{4}$") bore polythene tube connected the closed circuit to the inside of a float made of 1/16"(0.16 cm.) thickness perspex which was mounted over silicone fluid in a perspex tank. The float capacity was about 600 cc. A longitudinal section (Fig. 13) shows that the ends of the float form arcs of two concentric circles and equal segments of float contain equal volumes of gas. Two 1 cm. ($\frac{3}{8}$") bore perspex tubes connected the gas above the silicone fluid with the circuit and with the differentiating float. Another was connected to a pressure gauge which measured the pressure within the float.

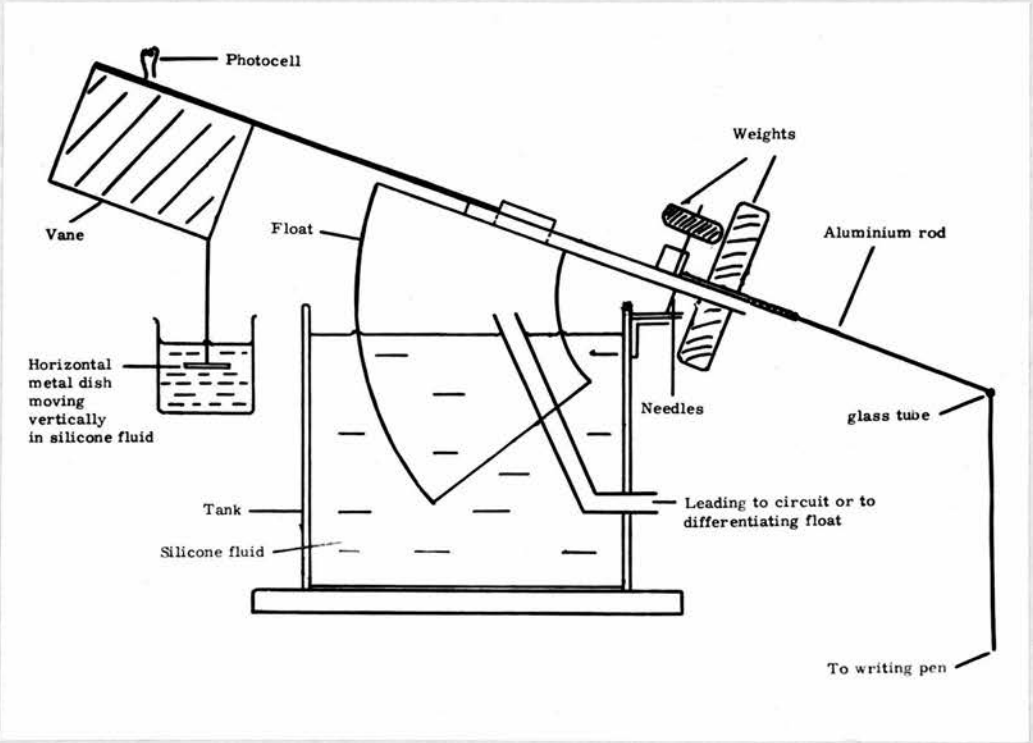


Fig. 13. Longitudinal section through circuit float.

For description see text.

Apparatus (cont'd).

Two perspex strips secured to the top of the float projected over the sides of the tank and in them were mounted two small gramophone needles which rested on a metal support. On these two needles the whole of the float was balanced. Weights were placed directly over both needles so that the float would balance at any angle.

A perspex cross bar was attached to each of the perspex strips and a screw with an adjustable weight was mounted in the centre of it. The position of the weight was adjusted until the float was accurately counterbalanced and the gas inside it was at atmospheric pressure. An aluminium rod was attached to the screw and a pen was suspended from a glass tube mounted at right angles to its end. The movements of the float were recorded continuously on kymograph paper.

The float was kept as light as possible to diminish inertia and to maintain sensitivity. The counter balancing weight was designed to be heavier and nearer the fulcrum rather than light and distant from it. (The moment of inertia is proportional to the square of the distance of weights from the fulcrum).

On the opposite side of the needles on which the float balanced another aluminium rod was attached to the top of the float. On the end furthest away from the needles it carried a vane of double thickness black paper. The vane was arranged so that at certain positions of the float it cut off a beam of light falling on a photo-electric cell. As the circuit volume diminished the float and vane descended and ceased to obstruct the path of light to the photocell. Light activated the cell to open an electromagnetic valve which allowed oxygen to pass from the differentiating float to the circuit. As the circuit volume was increased the vane rose to cut off

Apparatus (cont'd).

the light to the photocell and thus the inflow of oxygen. With this technique the sensitivity of the system was such that it responded to the removal of 2 cc. of gas from the circuit and the float moved in a series of small oscillations which were not visible to the naked eye. The photocell was so sensitive that a movement of the vane of less than 1 mm was able to activate it.

Crying and activity produced transient pressure changes and transient excesses of water vapour. These would have caused irregularities in the oxygen consumption record; the irregularities were reduced by damping the float movements by suspending a metal disc (1" diameter) from the lower angle of the vane and immersing it in silicone fluid. The disc was mounted horizontally and offered resistance to vertical movement through the fluid. The long piece of narrow tubing between the closed circuit and the float served the same purpose.

In addition transient pressure changes were absorbed by the insertion of a buffer float. This consisted of a perspex float similar to the circuit float, mounted over silicone fluid and similarly counter balanced, so that the gas inside was at atmospheric pressure. It was joined to the closed circuit. Sudden increases in circuit volume caused by the transient excess of humidity from a prolonged cry, first affected the buffer, and increases in volume caused it to rise. Similarly transient decreases in volume caused the buffer float to fall. This meant that the position of the circuit float was little altered and falsely low followed by falsely high measurements of oxygen consumption were avoided.

Apparatus (cont'd).

The Differentiating Float.

The differentiating float was a commercially available (C60A Palmer, London) volume recorder with a smaller capacity (about 30 mls.) than the circuit float but similarly shaped. A strip of Balsa wood 0.3 cm. ($\frac{1}{8}$") square was mounted on top of the float and at its end 8" from the fulcrum a horizontal glass tube was placed; a glass pointer was allowed to swing freely from the tube and carried a pen 18" below it. As the float emptied through the electromagnetic valve into the circuit float its movements were recorded by the pen as a line on kymograph paper.

At the end of a predetermined time (usually $\frac{1}{2}$ min.) the float was automatically refilled and the record appeared as a series of spikes; the length of each represented the oxygen consumption in the $\frac{1}{2}$ minute period.

On the opposite side of the fulcrum another balsa pointer projected carrying a vane at its end. Two phototransistors, an upper and a lower, were mounted so that the vane interrupted the light beam when the float was full and when it was empty. If the oxygen consumption was greater than 30 mls. per $\frac{1}{2}$ minute the light to the "empty" lower phototransistor was cut off and the float was automatically filled early and then refilled again at the end of the $\frac{1}{2}$ minute.

The float was counter balanced so that the gas pressure within was 4 mm of water greater than atmospheric. This was enough to allow a free flow of gas to the circuit float but not enough to be a source of error (see under 'storage float').

Apparatus (cont'd).

Calibration. The movement of the recording pen was based on the vertical movement of the end of the pointer which itself moved in the arc of a circle. The volume changes of the float were proportional to the length of the arc and the angle through which the float was moved; for this reason the scale was not quite linear. The float calibration was checked by adding 2 and 5 ml units of air from a syringe into a side arm from the tube joining the differentiating to the circuit float. The syringe used for calibration was checked by adding 1 2 and 5 ml samples of water from it to a 10 ml measuring flask. This calibration was performed half way through the series of experiments and found to be exactly the same as previously.

The Storage Float.

The differentiating float was automatically refilled from the storage float (Fig. 14) which consisted of an aluminium bell suspended over silicone fluid and counter weighted so that the oxygen inside was at a pressure of 7 mm of water and would flow easily to the differentiating float. The slightly increased pressure meant that the volume was decreased by less than 0.1% - an insignificant amount.

An inner perspex cylinder fitting inside the aluminium bell was filled with silicone fluid which was entirely separate from that in the rest of the tank and had a different horizontal level. The fluid level in the inner cylinder was shown in a vertical perspex tube mounted at the side of the tank and connected to the inner cylinder by a pipe running through the base of the float. Altering the fluid level in the inner cylinder by pouring silicone

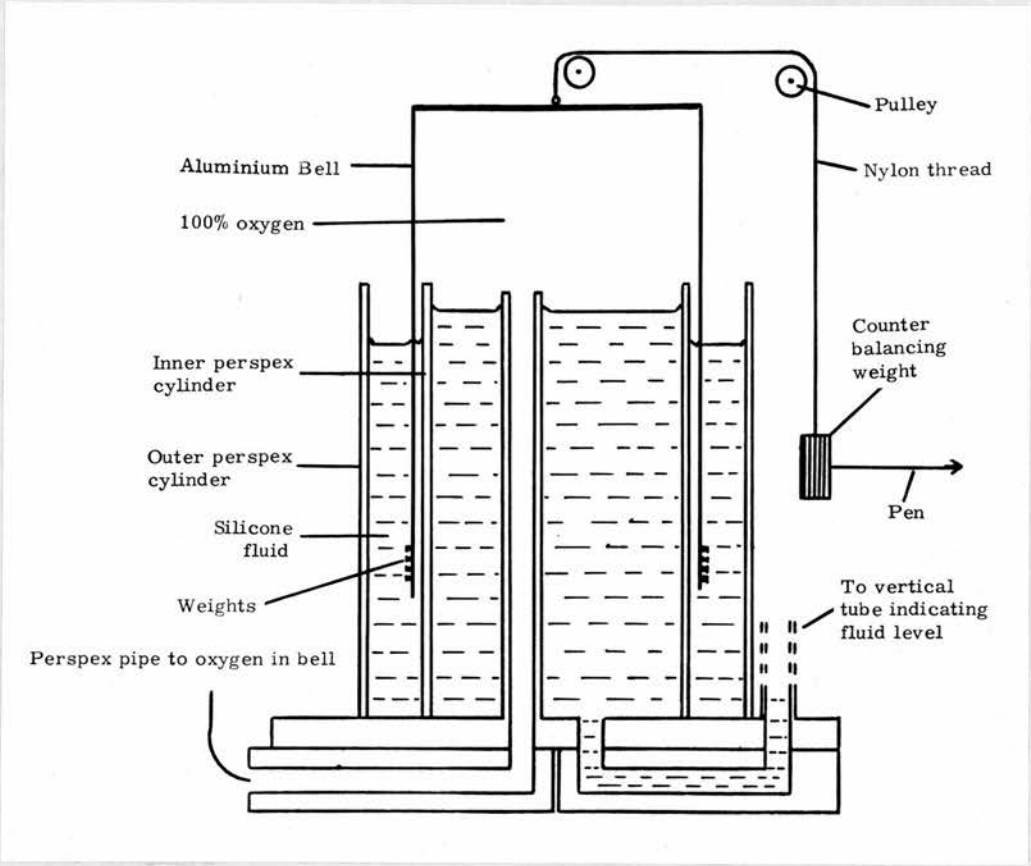


Fig. 14. STORAGE FLOAT: Vertical section.

The aluminium bell was suspended by a nylon thread which ran over pulleys to a counter-balancing weight on which the pen was mounted. The bell was weighted by split rings at its lower end and moved between an inner perspex cylinder which was filled with silicone fluid, and an outer cylinder. Channels in the perspex base conducted oxygen to and from the space under the bell.

Apparatus (cont'd).

fluid into the vertical tube altered the amount of dead space under the bell. Three other tubes passed in through the base and silicone fluid to the overlying oxygen; two channelled oxygen into and out of the float and the third was connected to a water manometer.

The storage float was refilled by hand from a cylinder of 100% oxygen and any traces of moisture were removed by first passing it through a tube of calcium chloride.

The recording pen was attached to the counter weight and the trace appeared as a series of steps; the up stroke represented empying into the differentiating tank and the trace was horizontal while the float was stationary. The proportions of the float were such that a pen movement of 1 mm represented a loss of 10 ccs of oxygen.

The Electromagnetic Valves.

The arrangement of the valves between the storage, differentiating and circuit floats is shown in Fig. 15. Valve 1 between the circuit and differentiating floats was controlled by the vane and photocell of the circuit float. (Electrical circuit 1 - see Fig. 16). When it opened it allowed oxygen to pass from the differentiating float via valve 3 into the circuit float.

Valve 2 allowed oxygen to pass from the storage float to the differentiating float. It was usually closed but was opened for a short time at preset ($\frac{1}{8}$ min.) intervals, or when the differentiating float was empty and was made to close when the differentiating float was full.

Valve 3 was simply an extension of valve 2 and it governed the flow of oxygen between the differentiating

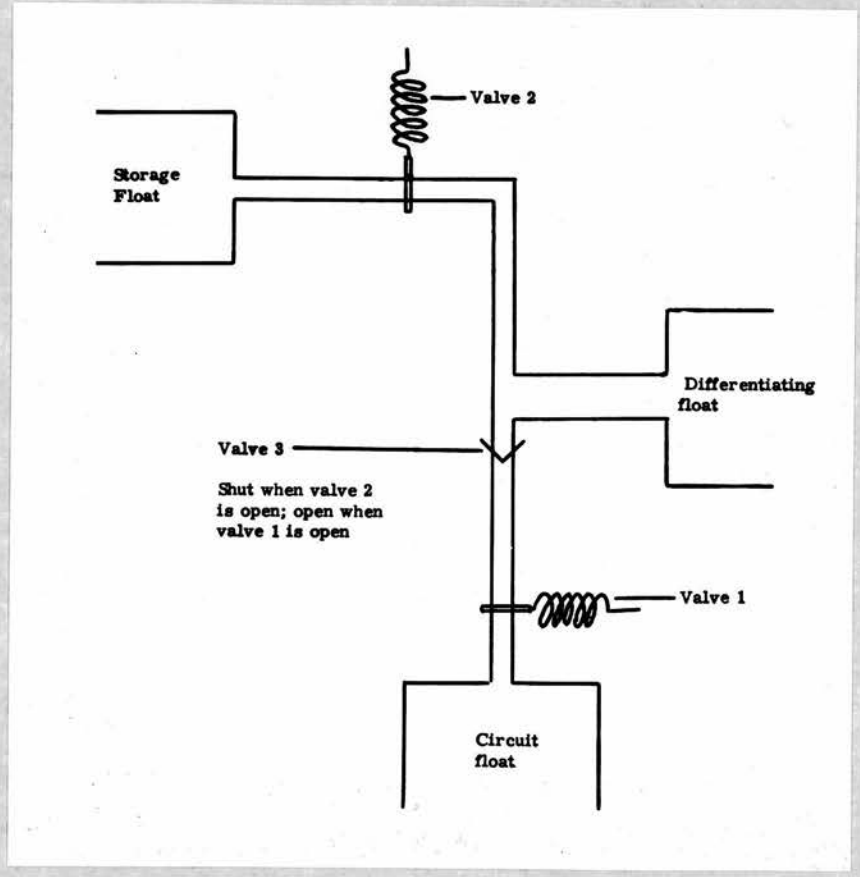


Fig. 15. Arrangement of valves between Storage, Differentiating and Circuit floats.

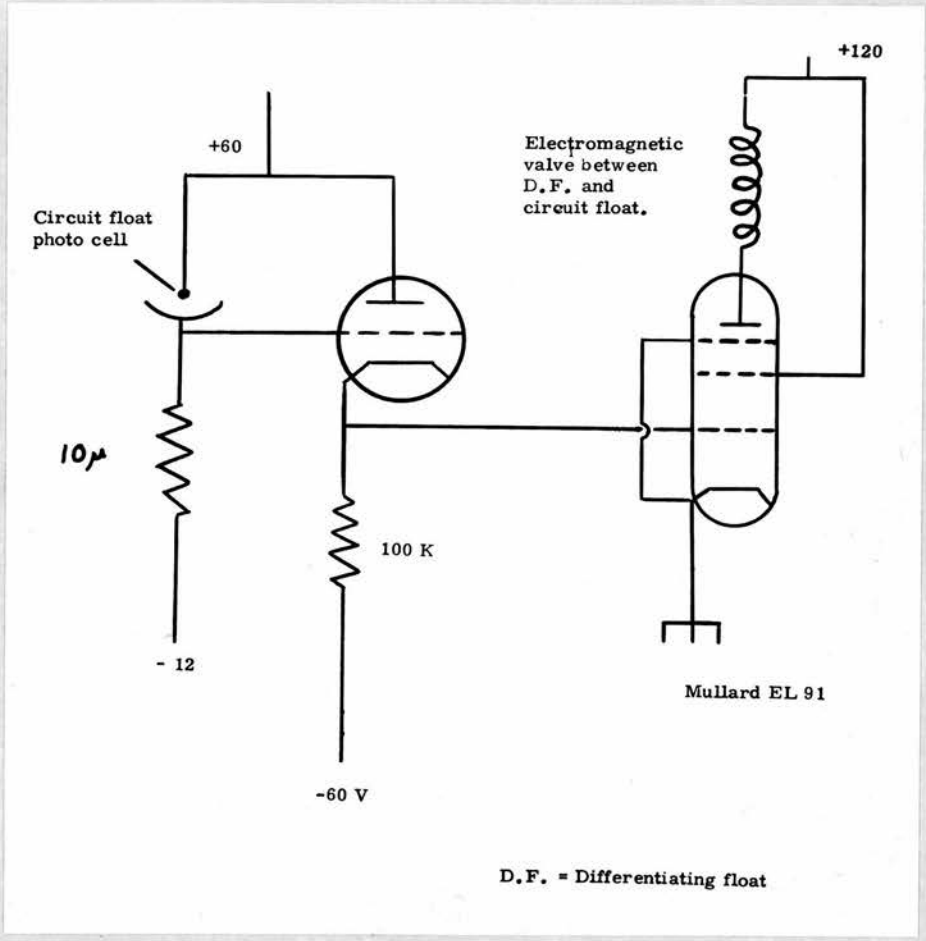


Fig. 16. Circuit (1) for circuit float photocell and valve from differentiating float to circuit float.

Apparatus (cont'd).

float and valve 1 and the circuit float. Valve 3 always acted in the opposite direction to valve 2 so that it closed when valve 2 was open and opened when valve 2 was shut.

As valve 2 was usually closed, valve 3 was usually open and allowed the differentiating float to empty freely. Valve 3 closed only during the short time when the differentiating float was being filled from the storage float and then acted to prevent the differentiating float from emptying and to prevent oxygen passing unmeasured through the differentiating float to the circuit float. Both valves 2 and 3 were controlled by electrical circuit 2 (Fig. 17).

Both valves were similar; when in the closed position small soft iron bars were pressed by springs onto soft rubber tubing and blocked the passage of oxygen. In the open position the electromagnets attracted the iron away from the rubber, and allowed a free flow of oxygen.

Electrical Circuits.

Electrical circuit 1, which was activated by the circuit float photocell, is shown in Fig. 16. The circuits 2A and 2B controlling valves 2 and 3 of Fig.15 are shown in Fig. 17. When the circuit 2A was made Y operated a slave relay (5) which made circuit 2B and operated the electromagnetic valve 2 between the storage float and the differentiating float. In circuit 2A, (4) the upper photo transistor of the differentiating float was usually at make. (It broke the circuit only when the differentiating float was full). Either (2) the lower photo transister which was at make when the differentiating float was empty or (1) the time clock

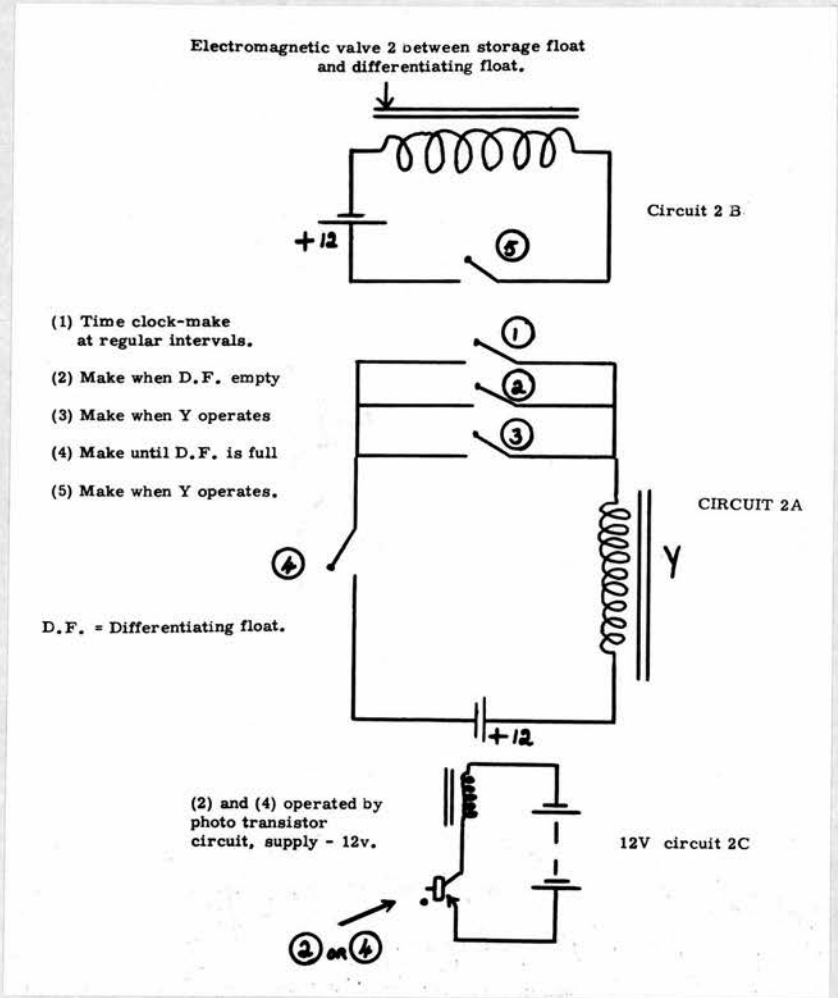


Fig. 17. Electrical circuits for electromagnetic valve between storage and differentiating floats.

Apparatus (cont'd).

which made for a short time at preset intervals, were the prime movers to switch on Y. When Y was operating it also made at (3) (a holdon - a Post Office relay). This was inserted because when (1) and (2) were broken after their brief makes Y would have collapsed if it were not held on by (3), and the circuit would have broken again after a brief make from the time clock or would have oscillated indefinitely about empty position. When the tank was filling (4) was made but broke the circuit through Y and (3) when the tank was full. As soon as the tank began to empty (4) made but each of the three contacts 1, 2 and 3 were at break and Y could not be operated; gas continued to pass as required from the differentiating float to the circuit float while the storage float remained stationary. This state of affairs existed until the end of the preset time interval or until the differentiating float emptied whichever was the sooner.

Sources of Error.

Any factor other than the consumption of oxygen which influenced the volume was a source of error. The accumulation of carbon dioxide and water vapour, fluctuation in the pump output and changes in volume due to crying have been considered. The detection of leaks is considered under methods. The water bath temperature was stable to within 0.05°C and the temperature of the room to which the rest of the apparatus was exposed changed by less than 1°C in the course of the whole experiment. Changes during 10 minutes were unlikely to be of any significance. Likewise changes in atmospheric pressure were negligible. Impurities in the oxygen content of the cylinder did not affect the result since the gas added, whether 100% or not, was counted as pure oxygen.

METHODS

Leak testing.

The pump was run for 20-30 minutes before the start of an experiment to allow thermal equilibration. About 200 mls of gas was removed from the closed circuit as a rough check that oxygen was being added and to remove oxygen left overnight in the polythene tubing from the storage tank. (Polythene is slightly permeable to oxygen). When the water bath had been set at the required temperature, and the temperatures of the thermo-couples measuring dry and wet bulb depression temperatures had settled, an unweighted leak test was performed for at least five minutes to ensure that there were no leaks into the circuit. After this a weighted leak test was performed with a 200 G weight placed on the circuit float to raise the pressure to greater than atmospheric. This was to ensure that there was no leak out of the circuit. The barometric pressure was taken and the room temperature was measured.

Preparation of the infant.

The infant was collected from the ward as soon as possible after a feed and weighed naked. Only full term normal infants without clinical abnormalities were investigated in the 15% oxygen project. A "Chironseal" urine collecting bag was put over the perineum to prevent additional heat loss from evaporation of the urine from the skin. The rectal thermo-couple was inserted to a depth of 5-10 cm and secured with adhesive strapping; the baby was slid into the chamber which was then closed with the perspex end plate.

A clock was started at the beginning of the experiments and marks made on the kymograph and six channel recorder paper so that records could later be keyed together.

Methods (cont'd).

Room temperature.

It was important to have a constant room temperature during the experiments so that the temperature of the gas added to the closed circuit was both known and constant. To maintain a constant room temperature it was usually necessary to cool the room by varying amounts depending on the weather outside, and sometimes necessary to warm it.

We had available an air conditioner which delivered a fixed amount of cool air and found that it was usually necessary to add varying amounts of heat to the room. On cold days the air conditioner was switched off. The major part of the warming of the room was done by a convector heater (adjustable to 3 kilo watts) but the fine control of the amount of heat added was simply but very effectively provided by a row of 100 watt electric light bulbs.

The room temperature was taken every 10 minutes. If it fell by more than 0.05°C another bulb was switched on, and if it rose by more than 0.05°C a bulb was switched off. If a visitor came into the room 1 or 2 bulbs depending on how active he was were switched off. With this technique the room temperature was maintained constant to within $\pm$ 0.5°C during each experiment.

At 10 minute intervals the temperatures of the water bath, the condenser and the room air were checked and recorded; the oxygen concentration in the apparatus and the flow rate were also recorded every 10 minutes.

Assessment of Activity

The infant was constantly observed and the activity during intervals of 2 minutes was recorded according to

Methods (cont'd).

the following scale:

1). Sleeping or inactive or with only an occasional jerk.
2). Awake and moving arms and legs.
3). Mild crying with almost continuous movement of arms and legs.
4). Crying lustily and moving hands and legs vigorously.
5). Maximal activity and howling.

Alteration of environmental temperature.

The temperature of the environment around the infant was controlled by the water-jacket temperature and the arrangements for changing the water temperature have already been described. After the environmental temperature was raised or lowered the records of the six channel recorder were scrutinised to ensure that the gas temperature had settled at the new value. Stabilisation at the new level occurred within 3 to 4 minutes after small changes in environmental temperature of about 2-4°C but after larger changes of 6-8°C the temperatures did not stabilise for several minutes. Such large changes were necessary in some experiments, (see Results: clothed babies) and these records were scrutinised with particular care. Measurements of oxygen consumption were only accepted as valid when the dry thermocouple temperatures had settled to within 0.5-1°C of their final level.

Alteration of oxygen concentration.

The percentage of oxygen was lowered by opening the circuit and by running in either 15% oxygen at 11 litres per minute for 2½ minutes approximately, or 5 or 10% oxygen for shorter periods of time. At least 3 minutes

Methods (cont'd).

was allowed for equilibration after the low oxygen mixture was added. The precise concentration of oxygen varied slightly but this did not appear to affect the results. The concentration of oxygen was raised by letting air into the circuit with or without additional oxygen.

Calculation of results.

A typical strip of experimental record is shown in Fig. 19. The fact that repeated measurements of oxygen consumption at ½ minute intervals were made, made it possible to establish the mean and confidence limits for any given period of time. The mean oxygen consumption over a 10 minute period was usually calculated and the use of 20 measurements to arrive at the mean gave it a precision of between 2 and 6%, (S.E.M./mean where S.E.M. is standard error of the mean).

Although Brück (1961) considered that it was necessary to measure the mean oxygen consumption during periods of 5 minutes because of the liability of restlessness to increase oxygen consumption, we found that 10 minutes was a satisfactory length of time as did Oliver and Karlberg (1963). The total metabolism during a 10 minute period is so large as to completely overshadow any change in oxygen store (Rahn, 1964), although this is not the case for carbon dioxide, (see Hill and Rahimtulla, 1965).

The length of the differentiating float spikes was measured against a scale obtained by direct calibration of the differentiating float. For ease of measurement this scale was modified slightly (see Appendix 1).

Methods (cont'd).

The results from the storage float and the differentiating float were always compared and agreement was always within 5%. The gas volumes were expressed at N.T.P. dry (Temperature: 0^{o} Centigrade and Pressure: 760 mm Hg., Dry.) The total oxygen consumption was divided by the body weight in kilograms to give the mean oxygen consumption in a 10 minute period expressed as mls/min. Kg. The 95% confidence limits of the mean were calculated from the standard deviation.

Ethical considerations.

Before the project was started it was thoroughly discussed with the Consultant Obstetricians and Paediatricians in charge of the babies, and their consent was willingly given. Before each baby was examined the nature of the investigation to be performed was carefully explained to the mother and her consent obtained. When convenient, or at the mother's request, the investigation was explained to the father also. It was found advisable to refer to each investigation as an investigation or as a "test" depending on the sophistication of the mother. The term "experiment" has very unfortunate connotations to the lay public and was never used.

15% oxygen has been shown to be without harmful effects and its use has been advocated therapeutically for premature infants (see Discussion). In general babies are not cyanosed in 15% oxygen. The pO_2 in the arterial blood of infants breathing 15% O_2 in N_2 (about 50 mm Hg., Graham, 1959) is greater than the pO_2 in the umbilical vein a few seconds after birth 35-40 mm Hg. (Karlberg and Colander, 1965). It is also helpful to consider that the partial pressure of oxygen in 15% oxygen in nitrogen at

Methods (cont'd).

atmospheric pressure is the same as that in air at about 8,500 feet. (Mexico City, altitude 7,575 ft. is "equivalent" in oxygen tension to 15.5% O_2, see Introduction; Denver, Colorado altitude 5,000 ft. is "equivalent" to 17.25% O_2, see Van Liere, 1942).

CHAPTER 3
RESULTS

CONTENTS OF RESULTS

CONTENTS OF RESULTS CONT'D.

RESULTS

Introduction and Metabolic Response to Cold.

Some preliminary experiments were performed to illustrate the theoretical relationship between environmental temperature (Te) and oxygen consumption, which is shown in diagrammatic form in Fig. 18 and mentioned on page 92 . In Fig. 19 is an untouched photograph of a typical experimental record showing oxygen consumption in a naked baby. In Fig. 20 the results are plotted out. There was a definite increase in oxygen consumption as the environmental temperature was lowered. Between 36°C and 32°C there was little change in oxygen consumption indicating the thermo neutral range but a clear rise was recorded at 28°C which was increased at 24°C where the oxygen consumption doubled. The experimental record shows that the rise occurred in the three or four minutes taken by the apparatus to stabilise at the new temperature and that the rate of oxygen consumption was maintained constant at its new level. When the environmental temperature was increased there was an immediate fall in oxygen consumption.

These changes took place long before any change in rectal temperature and suggest that deep body temperature is not of immediate importance in regulating heat production in these circumstances. In fact the rectal temperature was high when oxygen consumption increased and low when it fell: the converse of what one would expect if rectal or deep body temperature regulated oxygen consumption. The rectal temperature at an environmental temperature of 28°C was higher than at Te 36°C although the oxygen consumption was increasing; the initial rectal temperature at Te 24°C when oxygen

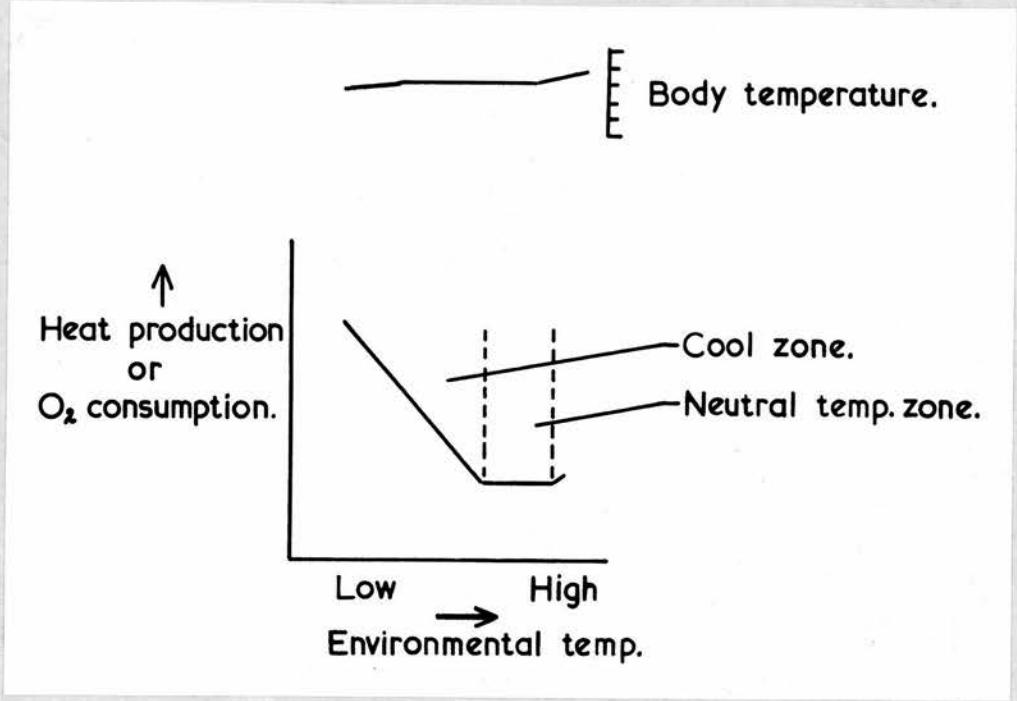


Fig. 18. Schematic representation of the relations between oxygen consumption, environmental temperature and body temperature. The sloping part of the line for oxygen consumption represents the metabolic response to cold, and the horizontal part the basal metabolic rate. The junction between the horizontal and sloping lines is the critical temperature.

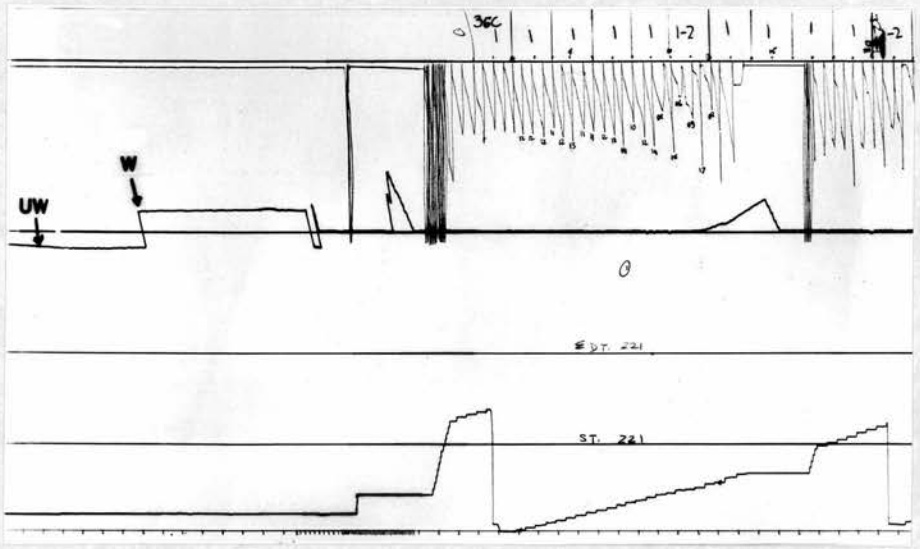


Fig. 19(a)

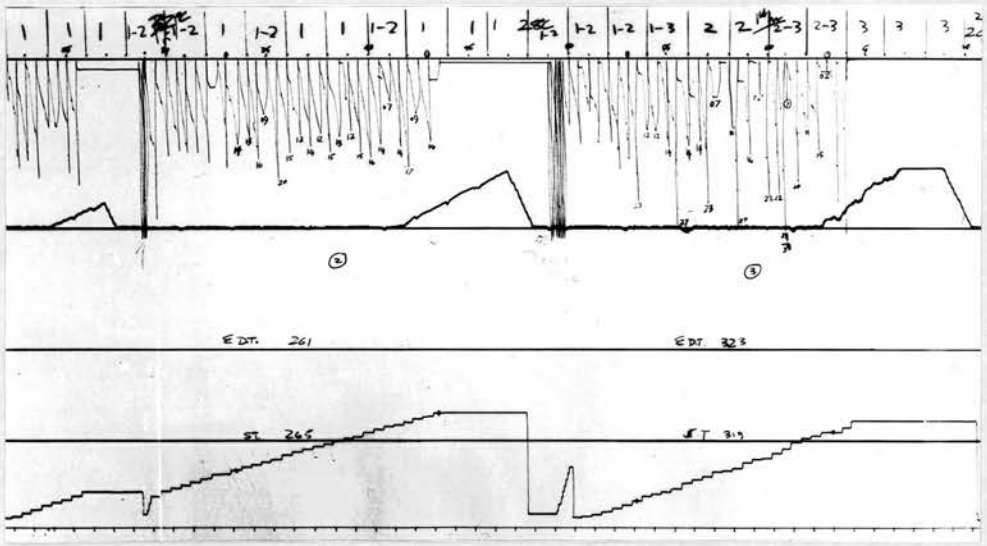


Fig. 19(b)

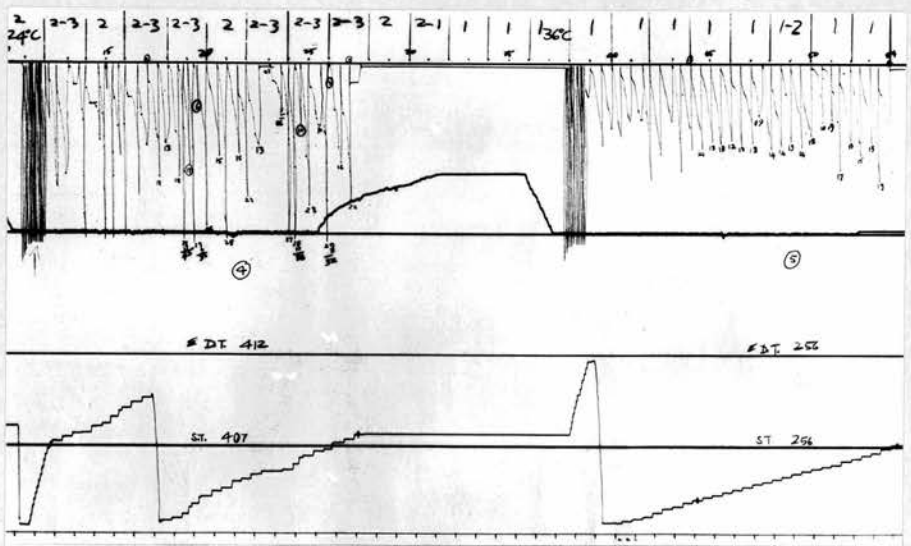


Fig. 19(c)

Fig. 19 (a, b, c).

Strip of Untouched Experimental Record (65C)

Upper tracing - differentiating float record
leak tests (W = weighted
(UW = unweighted

Middle tracing - circuit float record

Lower tracing - storage float record

Bottom tracing - time 1 min. intervals

The top row of figures represents the activity in arbitary units. Figures beneath the differentiating float record indicate oxygen consumption in each ½ minute. $\mathcal{E}$D.T. indicates total volume of oxygen discharged from the differentiating float in the 10 minute period considered. S.T. is the total volume of oxygen discharged from the storage float in 10 minutes. These two volumes agree to within 3%.

The environmental temperatures are indicated with the figures for activity, and the environmental temperature in period (4) was 24°C.

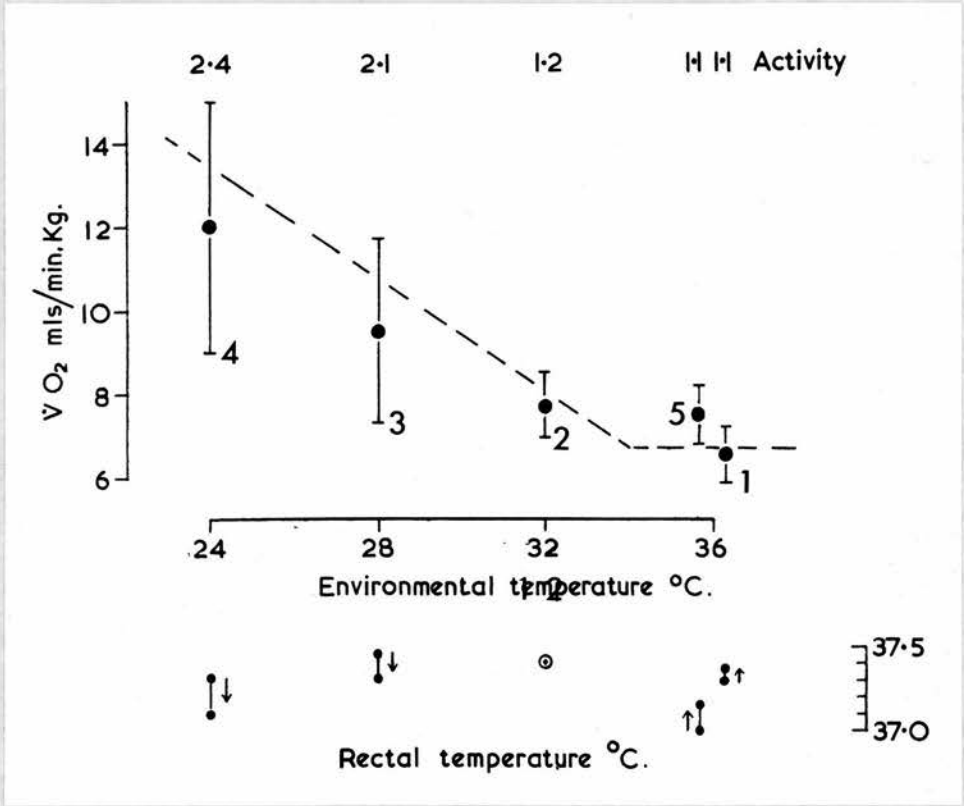


Fig. 20

Mean oxygen consumption in mls/min. Kg., with 95% confidence limits of mean ($\overset{\top}{\perp}$) at different environmental temperatures, in a 2 day old normal infant, weight 3.03 Kg. Small figures indicate order of measurements. Bottom graph shows simultaneous rectal temperatures (↑ rise, ↓ fall). The dotted line indicates the results for a 2 day old infant of Hill & Rahimtulla (1965) (Fig. 3(c)) for the basal oxygen consumption in the thermo-neutral zone (horizontal), and the response of oxygen consumption to environmental temperature (sloping). The junction of the two lines is the critical temperature.

Results (cont'd).

consumption was highest was still greater than that at Te 36°C. Conversely at the second measurement at 36°C the rectal temperature was lower than it was at 24°C.

The baby increased its metabolic rate as the temperature was lowered, but the increase was insufficient to maintain it in heat balance although less than the possible maximum; at lower environmental temperatures the rectal temperature fell. At Te 28°C the rectal temperature was falling even though maximum oxygen consumption had not been reached. It appears that the infant does not produce an adequate increase in oxygen consumption although it is potentially capable of so doing; the inadequate response may occur in spite of falling rectal temperatures. The labile rectal temperature is much more marked in the first few days of life than later.

The fall in rectal temperature is further illustrated in the tables of the effect of 15% oxygen on the oxygen consumption in the cool, which demonstrate a fall in rectal temperature in the control periods, breathing air before 15% oxygen, even though the mean increase over the basal oxygen consumption was only 40%. At higher environmental temperatures the rectal temperature consistently rises, this too is shown later. /See sections on Effect of activity; effect of 15% oxygen in the warm/. Newborn rabbits behave in a similar manner (Mestyán, 1964).

Behaviour in a cool environment.

Figs. 19 and 20 show that the activity is low at higher temperatures, higher at lower temperatures and it rapidly falls when the environment is warmed. Some of the increase in metabolism in cool environments is due to the extra activity, but not all for in other

Results (cont'd).

experiments an increase in oxygen consumption was provoked without activity; also when the activity was constant the metabolic rate was lower in a warmer than in a cooler environment. The activity not only tends to be higher in cooler environments than in warmer ones but is also more variable; this proved later to be a difficulty when comparing oxygen consumption measurements in air and 15% oxygen.

The activity was closely observed and recorded every two minutes but it was not possible to correlate activity with oxygen consumption sufficiently precisely to be able to predict oxygen consumption in air at a particular high activity. In comparing metabolism in air and 15% oxygen the environment was cooled so that oxygen consumption increased but there was only minimal activity. A later section shows that slight degrees of activity have negligible effect on oxygen consumption. The younger the baby the easier it was to provoke an increase in oxygen consumption without increasing activity. We gained the impression that clothed babies tend to be less active than naked babies for the same increase in metabolism above the basal metabolic rate.

A detailed study of the neutral thermal range, critical point and the metabolic response to cold was made using the same apparatus before these experiments were performed. This study has been fully reported (Hill and Rahimtulla, 1965) and was not repeated.

However, the basal metabolic rate was estimated in nearly all the air and 15% oxygen experiments and some of the results are reported below.

THE BASAL METABOLIC RATE.

The definition that we adopted was "the rate of oxygen consumption while inactive in the thermal region

Results (cont'd).

where metabolic rate has reached a minimum and become independent of environmental temperature." (Hill, 1964). Only the systematic exploration of oxygen consumption at different environmental temperatures can delineate the cooler environmental temperatures at which metabolic rate is increased and their junction with the thermal region where the oxygen consumption has become basal i.e. minimum and no longer falls as the environmental temperature is raised. The definitions of basal metabolic rate and thermo-neutral zone are interdependent and actual values can be determined only by experiment. This has been done and published work (Hill and Rahimtulla, 1965) has indicated that in this apparatus the lower boundary of the "thermo-neutral zone" - that is the critical temperature - is about 34-37°C on the day of birth, falling to around about 30-33°C at seven to nine days. A value of about 34°C between the second and sixth and seventh day has been used. There is a marked variation in critical temperature between different babies and it is difficult to define critical temperature very closely.

In this section all the measurements of oxygen consumption in inactive normal babies at environmental temperatures greater than the critical have been considered. The lowest measurement of oxygen consumption obtained from each subject at a given age has been selected as the basal metabolic rate at that age. The basal metabolic rate will be discussed in relation to a number of different variables.

Basal Metabolic Rate and Weight.

This aspect is discussed first to elicit an important relationship which simplifies subsequent discussion. The basal metabolic rate expressed as millilitres of oxygen

Results (cont'd).

consumed per baby per minute, and body weight in kg., plotted in double logarithmic co-ordinates to illustrate possible relations between basal metabolic rate and a power of the body weight (e.g. body weight to the 2/3 power or body weight to the 3/4 power) are shown in Fig. 21. To eliminate the effect of age as a variable (see later) only babies of 2-13 days are considered in detail, and it has been shown by Hill and Rahimtulla (1965) that there is no significant change in the basal metabolic rate in this age range. The few babies aged less than 2 days are not included in this graph.

There is a close correlation between the two variables, and a line drawn by eye through the points does not differ significantly from the solid line in the diagram which has unit slope. Within the weight range considered the basal metabolic rate is directly proportional to the body weight. The same variables are plotted on a linear scale in Fig. 22 and the expected relationship is confirmed. ($r = 0.90$, P less than 0.001).

Both the regression lines of oxygen consumption on weight kg. and vice versa have been calculated by the least squares method.

One regression line of Fig. 22 passes very close to the origin, and it seems reasonable to assume that basal metabolic rate is directly proportional to body weight in the 2-13 days age group. In 7 results available in the 0-18 hour age group the same relationship is seen (Fig. 23). To facilitate comparison of infants of different weights all subsequent results are expressed as mls/min per kg.

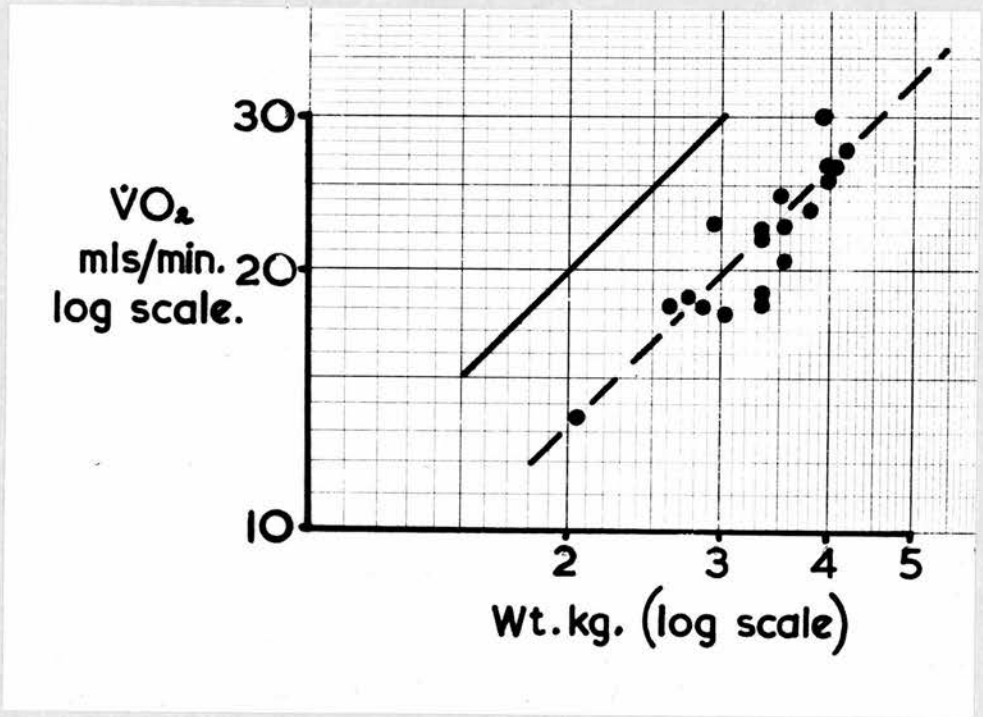


Fig. 21. Oxygen consumption and basal metabolic rate in double logarithmic coordinates.

On log scales basal metabolic rate in mls/O_2 min. and body weight Kg. in a group of 20 infants aged 2-13 days. Only 1 result is shown from each baby and if more than one result was available the lowest has been shown. One premature baby was included. The solid line indicates unit slope, and it is parallel to a line between the points drawn by eye.

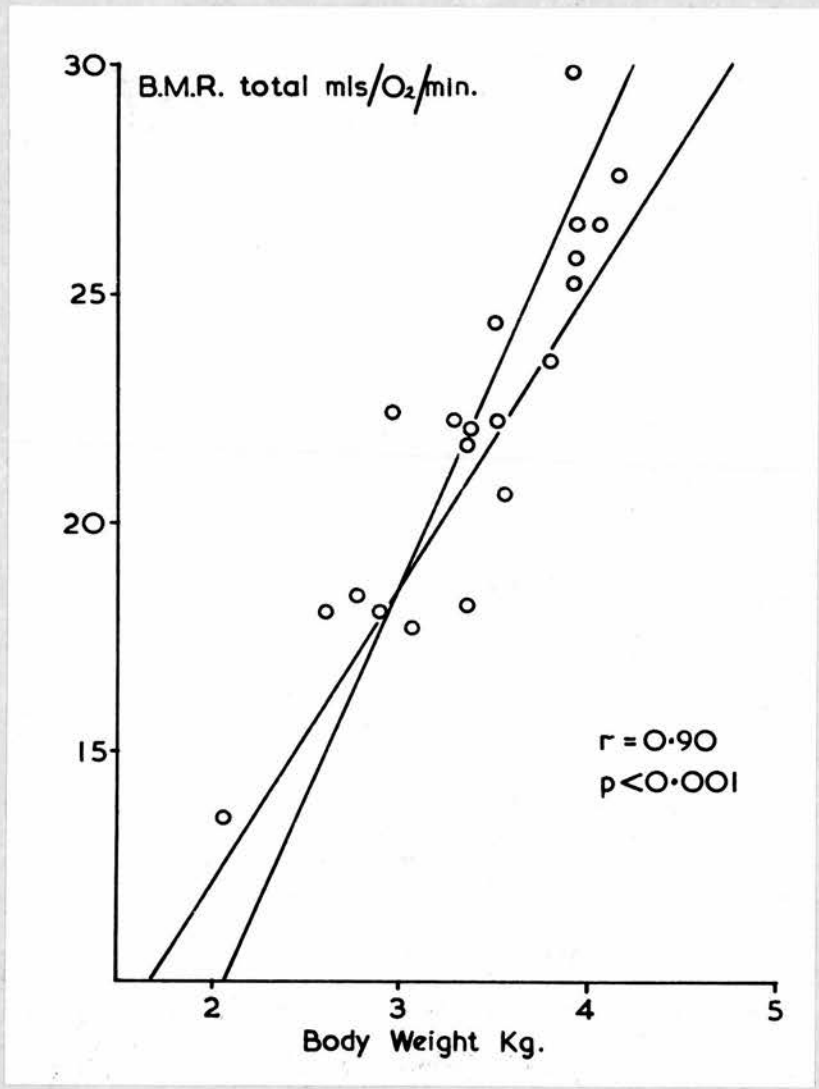


Fig. 22

Basal metabolic rate mls/O_2 per min. and body weight Kg; both on linear scales. Same infants and values as in Fig. 21. Both regression lines are shown and

$y = 7.27x - 2.52$

$x = 0.11y + 0.96$

$r = 0.90,\ p < 0.001.$

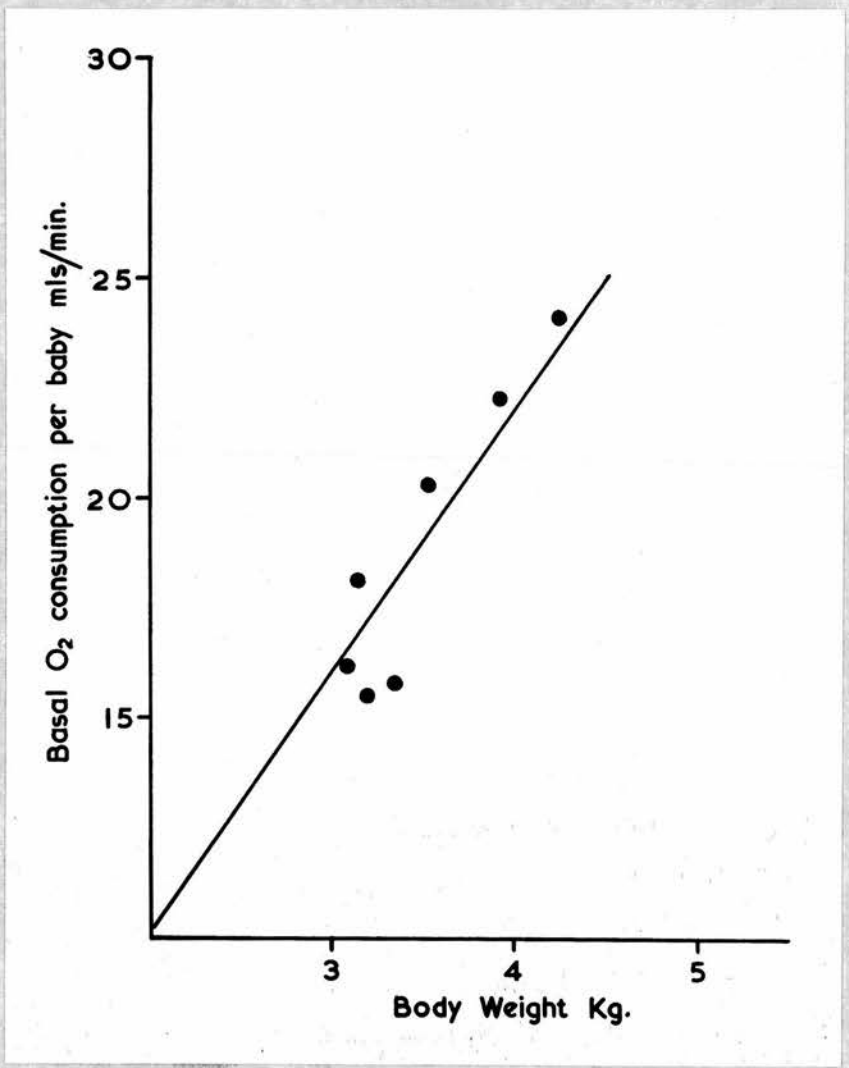


Fig. 23

Basal oxygen consumption and body weight in 7 babies aged 0-18 hours.

Results (cont'd).

This finding is similar to that of Karlberg (1952) for infants aged 1 week to 1 year and that of Hill and Rahimtulla, 1965, for babies aged 0-6 hours and 6-10 days. Inspection of the data of Adamsons, Gandy and James (1965) shows that when oxygen consumption was expressed per unit weight the babies of that study who were all aged less than 4 hours had much the same value for basal metabolic rate regardless of their size.

This result may be contrasted with that of Brody (1945), Kleiber (1961) and Hemmingsen (1960) who found that in a wide range of adult animals of different species (varying from adult mice to adult elephants) the basal metabolic rate was related to body weight to the power n where n lay between 0.70 and 0.75. In infants, and presumably in young animals of a given species the position is different and basal metabolic rate is related directly to body weight, i.e. to body weight to the power 1, or very nearly. Karlberg (1952) suggested that the higher exponent noted during infancy must be partly due to the influence of growth on energy metabolism.

Basal Metabolic Rate and Age (see Fig. 24).

The Basal Metabolic Rates of all the babies who were examined in the first 24 hours are lower than those in the second and subsequent days - in fact the four babies who were investigated both in the first 24 hours and subsequently all showed a rise in oxygen consumption and in three the rise exceeded the 95% confidence limits. (These results on younger babies are shown separately in Fig. 25).

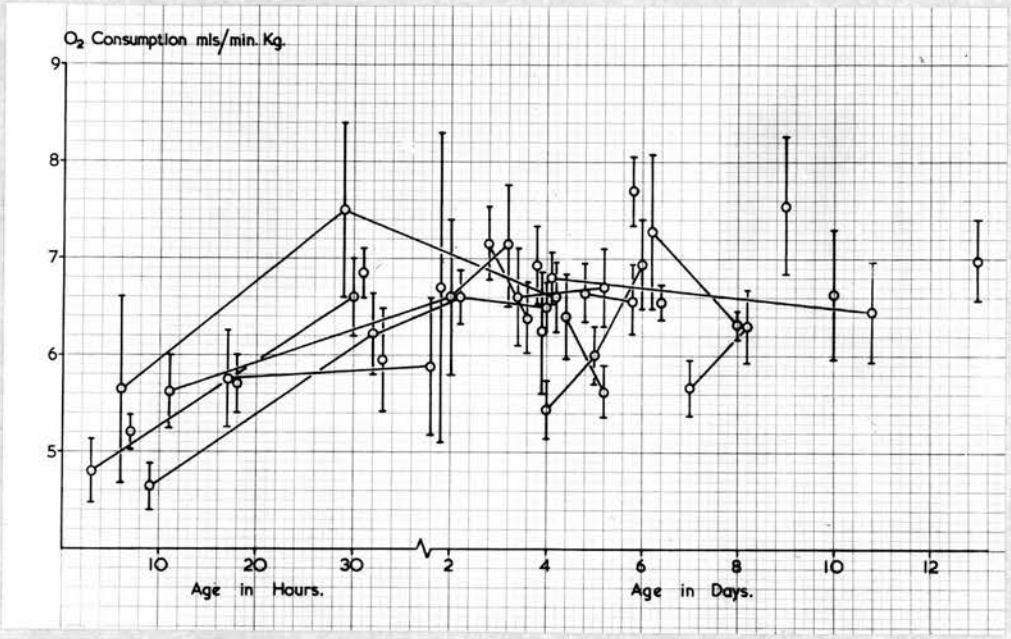


Fig. 24. Basal metabolic rate and age.

Basal oxygen consumption in mls O_2/min per Kg. on a continuous scale plotted against age on a changing time scale with alterations indicated by breaks in the abscissa. 43 estimations of basal metabolic rate from 25 different babies are shown. Again only inactive babies in the neutral temperature range have been considered and if more than one estimation of the basal metabolic rate was available at a given age only the lowest is shown. Measurements made on the same babies are joined by lines.

Symbols . indicates mean
indicates 95% confidence limits of mean

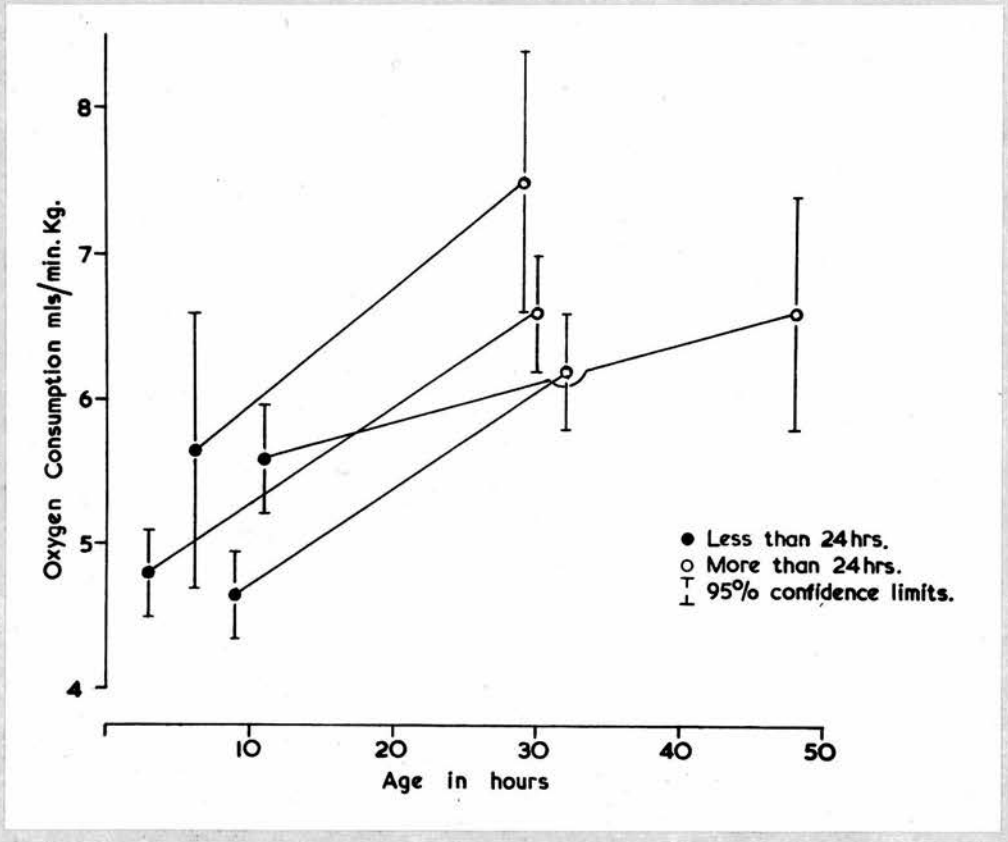


Fig. 25 Basal metabolic rate measured in 4 babies at ages less than and greater than 24 hours.

Results (cont'd).

From two days to thirteen days oxygen consumption remained fairly constant at values greater than earlier. There are some variations in individual babies examined on different occasions but these changes are probably within limits of expected error. The mean values are indicated in Table 1. where the later age groups are arranged to correspond with those of Hill and Rahimtulla (1965). The oxygen consumption appears to be lower in the first few hours, and there is a statistically significant difference between the basal oxygen consumption in the youngest age group and each of the other three. This agrees with the findings of Cross et al. (1957) and Hill and Rahimtulla (1965) who showed there was a highly significant rise in the basal metabolic rate much of which took place between the first 6 hours and 18 hours of life. Brück (1961) also found that there was an increase in basal metabolic rate of about 11% between the first, and second and third days of life. According to Taylor (1960) an increase in oxygen consumption shortly after birth has been found in all the mammalian species in which it has been investigated. The number of babies in the present study is not sufficient to establish the exact timing of the increase in the basal metabolic rate. This timing of the increase in basal metabolic rate applies only to full term, and not to premature, infants.

The reasons for this increase in metabolic rate are still uncertain but two factors that must be excluded as causes are the change in weight during the first few days and the change in rectal temperature.

TABLE 1

BASAL METABOLIC RATE IN FULL TERM NORMAL INFANTS

Age	n	Mean wt. Kg.	Mean basal oxygen consumption mls/min.Kg.	1 S.D.	1S.E.M.	Probability of difference from youngest group arising by chance
0-18 hrs	6	3.16	5.36	0.50	0.22	---
18-36 hrs	5	3.06	6.62	0.47	0.21	$0.01 > P > 0.001$
2- 4 days	12	3.68	6.64	0.42	0.12	$P < 0.001$
5-13 days	12	3.41	6.63	0.56	0.16	$P < 0.001$

Results (cont'd).

Change in Weight. The physiological loss of inert meconium, urine and body water during the first few days of life must be expected to cause an apparent increase in the metabolism per unit weight of the remaining body substance. But in the babies exemplified the actual change in weight is far smaller than the change in basal metabolic rate. Table 2 shows the changes in body weight to be of the order of 5% while the changes in basal metabolic rate are of the order of 15-30%. The changes in basal metabolic rate and weight occur at different times for the maximum weight loss does not occur until approximately the 3rd day while the change in basal metabolic rate is within the first 24 hours.

Rectal Temperature and Basal Metabolic Rate.

In Fig. 26a the same values for basal metabolic rate for the same babies as in Figs. 21 and 22 are plotted against the rectal temperatures at the time the measurements were made. Younger and older babies are grouped together but given distinguishing symbols. Again only the lowest metabolic rate value in either age group is shown and four babies were studied at both groups of ages.

As is expected there is fairly wide scatter of rectal temperatures between 35.5 and 37.5°C. The values for the five babies less than 24 hours tend to be lower than the others. There is no clear relationship between basal metabolic rate and rectal temperature. Both Mestyán, Varga, Fohl and Heim (1962), Mestyán, Fekete, Bata and Jarai (1964a) working with premature infants, and Hill and Rahimtulla (1965) (full term infants) found no evidence of a relationship between basal metabolic rate and

TABLE 2

INCREASE IN B.M.R. AND CHANGES IN BODY WEIGHT

Expt. No.	B.M.R. mls/min.Kg.			Weight Kg.		
	Age<24 hrs.	Age > 24 hrs.	% increase in B.M.R.	Wt. at age<24 hrs.	Wt. at age>24 hrs.	% Fall
64A	5.62	6.61	17.6%	3.93	3.90	1%
65A	4.80	6.60	37.5%	3.23	3.10	4%
66	4.64	6.22	34.1%	3.37	3.22	5%
69	5.64	6.61	17.2%	4.25	4.17	2%

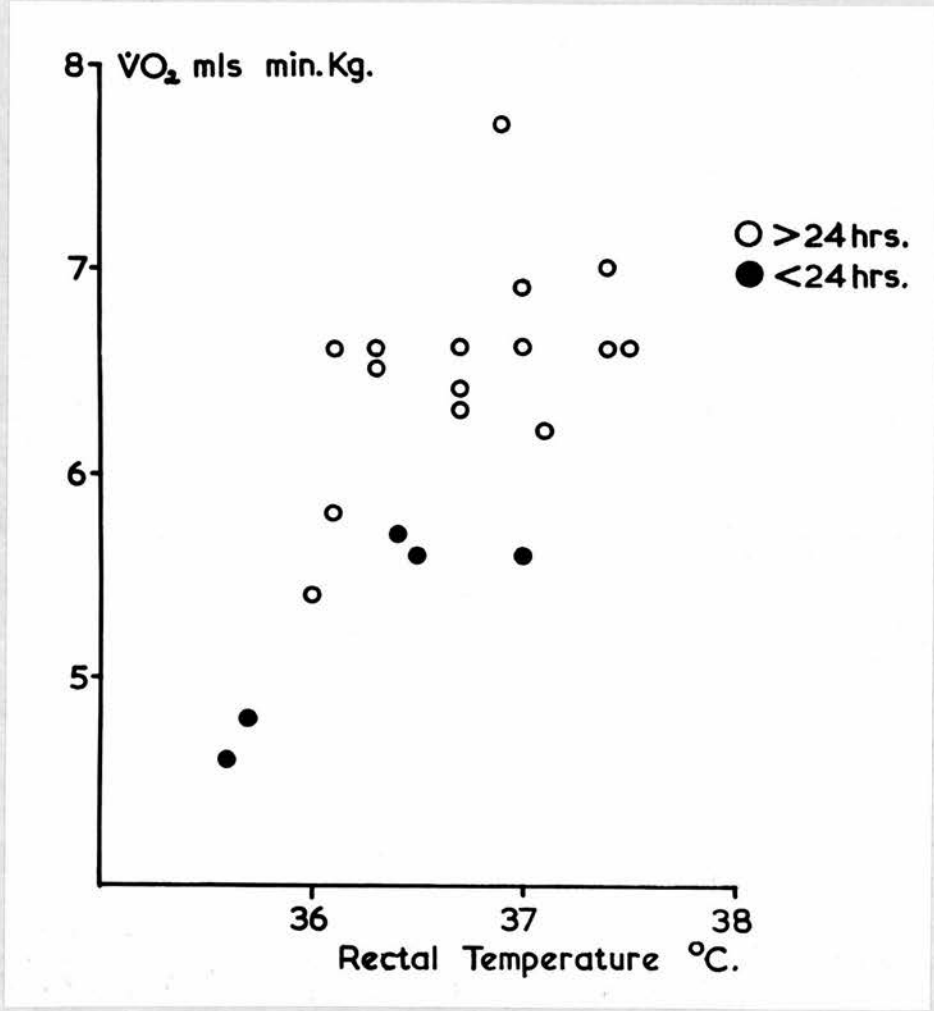


Fig. 26(a) Basal metabolic rate mls/min.Kg. and rectal temperature.

The values for oxygen consumption for babies aged over 24 hours are the same as those in Figs. 21 and 22 and those for babies less than 24 hours are as in Fig. 23. (The rectal temperature was not measured in 2 of the 7 subjects shown in Fig. 23 so that only 5 are included in this figure).

Results (cont'd).

rectal temperatures varying from 35-39°C (Mestyan et al., 1962) and from 35-38°C (Hill and Rahimtulla, 1965). In the results of Brück (1961) there is a wide variation in rectal temperatures with very little variation in basal metabolic rate. Likewise Adamsons et al. (1965) found no evidence of a relationship between basal metabolic rate and rectal temperature in a group of babies aged 0-4 hours.

In enzyme systems, isolated tissues and poikilothermic animals the relationship between the rate of a chemical reaction and the temperature of the system is described by the Q 10 effect, which states that the rate of a chemical reaction is approximately doubled or trebled by a rise of 10°C. (Wilkie, 1962). This is also true for homeothermic animals in severe hypothermia. Thus on this basis the lower the rectal temperature the lower the basal metabolic rate ought to be. The well known tendency for the infant to have a low rectal temperature in the first few hours suggests that the low basal metabolic rate at this time may be due simply to low body temperature. In view of this possibility the four babies who were examined both before and after 24 hours are shown in Fig. 26b. The rectal temperatures on a linear scale and basal oxygen consumption on a log. scale are again plotted. It will be seen that the rectal temperature in one baby was the same at both ages; calculation indicates that the mean Q 10 for the other 3 babies is approximately 170. This is very different from the usual value found in biological systems of about 2 or 3. It is concluded that the increase in basal oxygen consumption is not clearly due to a Q 10 effect but the temperature range is too small to exclude this concept completely. In any case the Q 10 effect does not amount

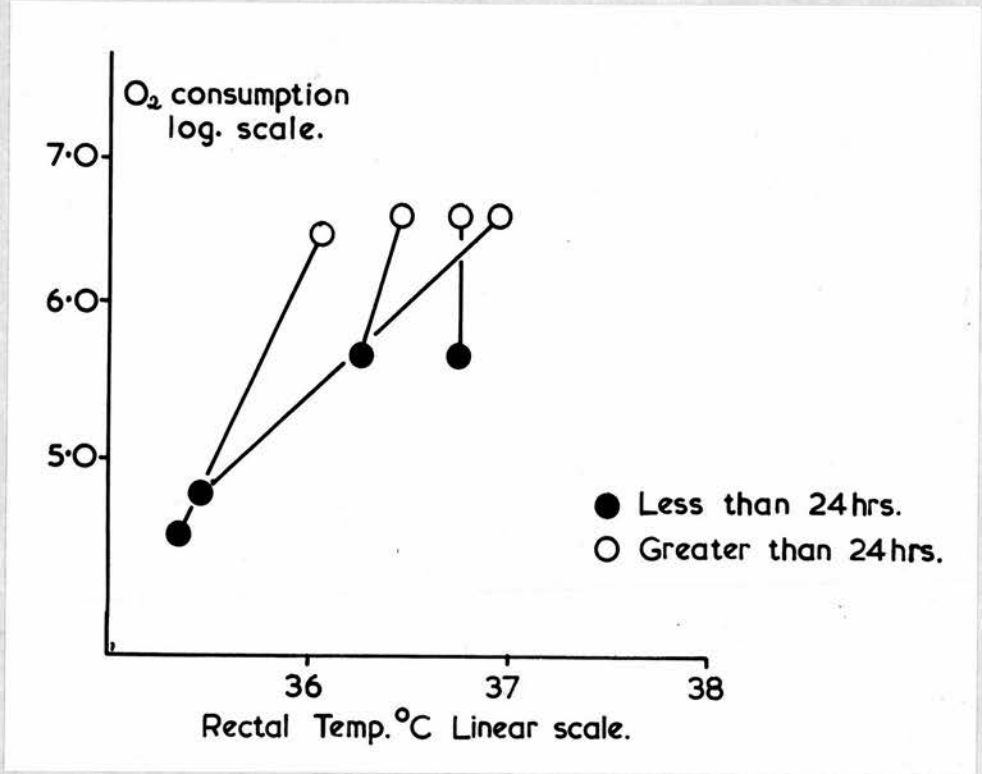


Fig. 26(b) O_2 consumption mls/min.Kg. (log scale) and rectal temperature (linear scale) in babies examined at ages less than and greater than 24 hours.

Results (cont'd).

to more than a 7-10% increase per degree centigrade change in body temperature and this may well be too small to demonstrate.

Further evidence is available from continuous measurements of oxygen consumption in the same baby over a period of about half an hour when the rectal temperature was simultaneously recorded. Fig. 27 (a-e) shows that small changes in rectal temperature can occur while the oxygen consumption more or less remains constant. All the babies were in environmental temperatures greater than the critical and were in the thermo-neutral zone.

Adams, Fugjwara, Spears and Hodgman (1964) interpreted their data on basal oxygen consumption in premature infants as showing evidence of a Q 10 effect but both Mestyán et al. (1964a) and Adamsons et al. (1965) strongly criticised this view. However, Cross, Hill and Robinson (1965) showed clear evidence of a Q 10 effect in an anencephalic baby who was much colder than the infants considered here, and Hey and Lewis (unpublished observations) have demonstrated the same in a baby recovering from cold injury.

Basal Metabolic Rate and Feeding.

Measurements of the basal metabolic rate in adults are preceeded by overnight fasting because food has a specific dynamic action. Fasting is not practical in newborn babies: a hungry baby is restless and cries (sedation is certainly undesirable).

All the results on babies in whom the basal metabolic rate was estimated at the beginning and end of the experiments were examined for evidence of a change in oxygen consumption. In Fig. 28 which gives

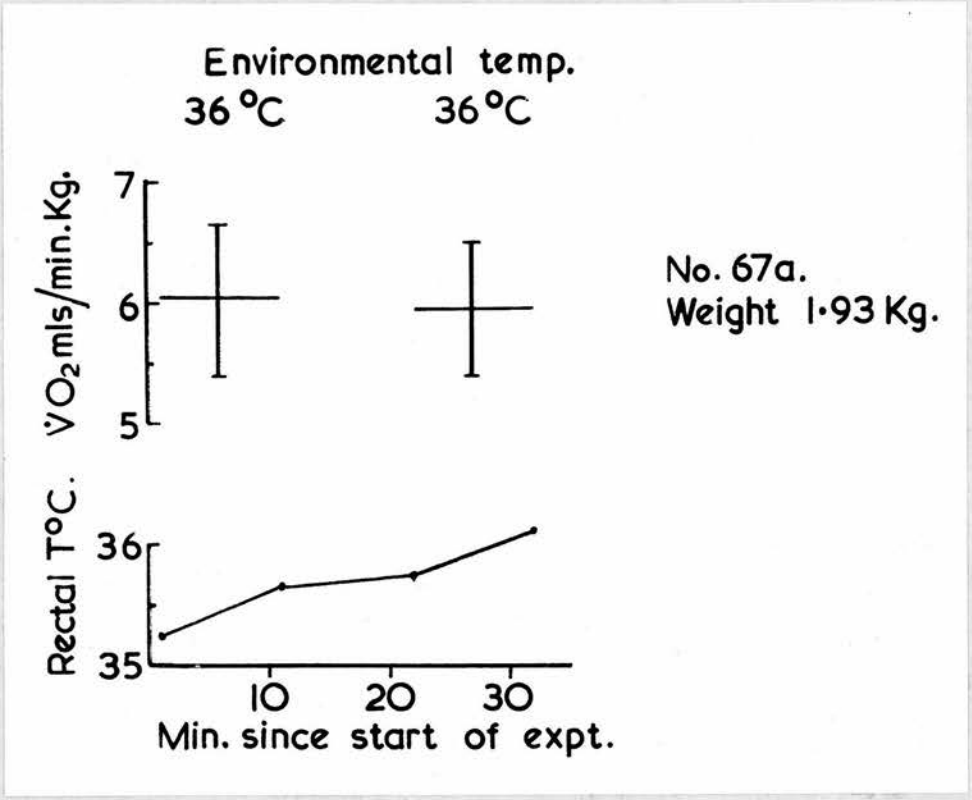


Fig. 27a.

Fig. 27 a, b, c, d, e. Measurements of oxygen consumption over 10 minute periods (——— = mean and ⊤⊥ 95% confidence limits of mean) in babies in neutral temperature zone with simultaneous measurements of rectal temperature.

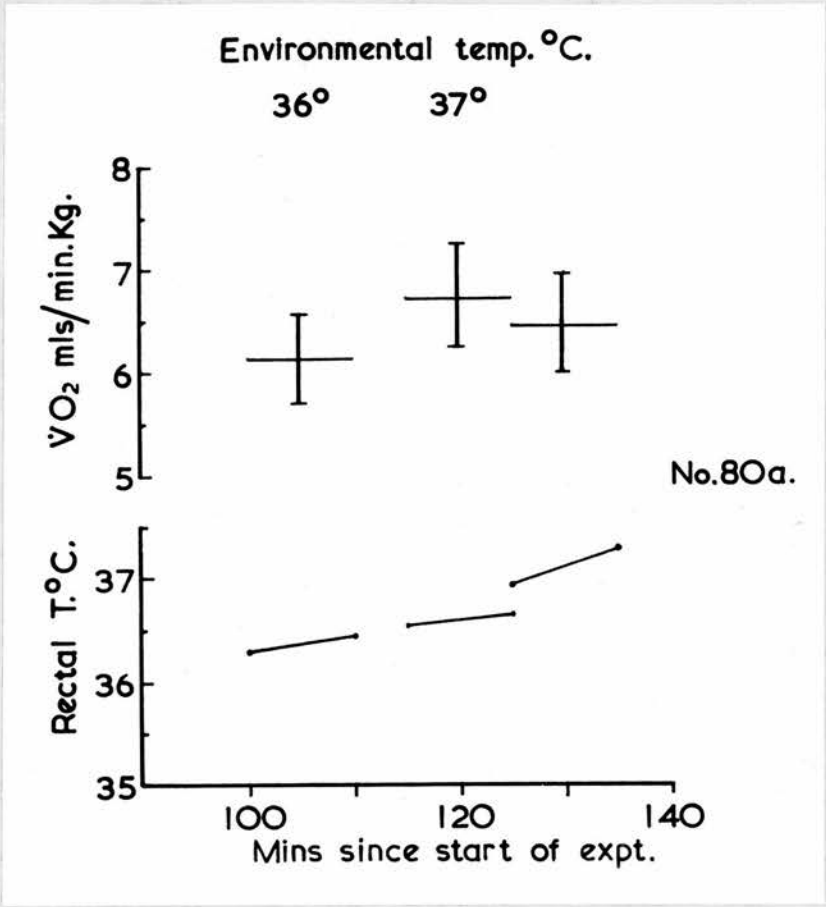


Fig. 27b

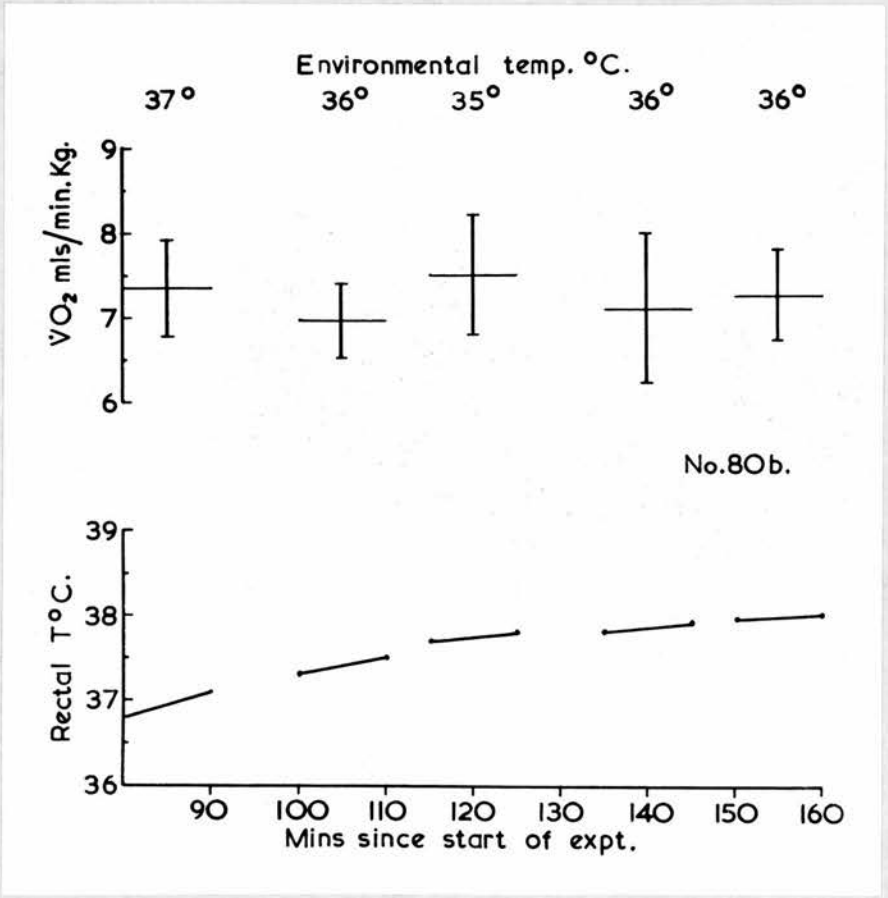


Fig. 27c

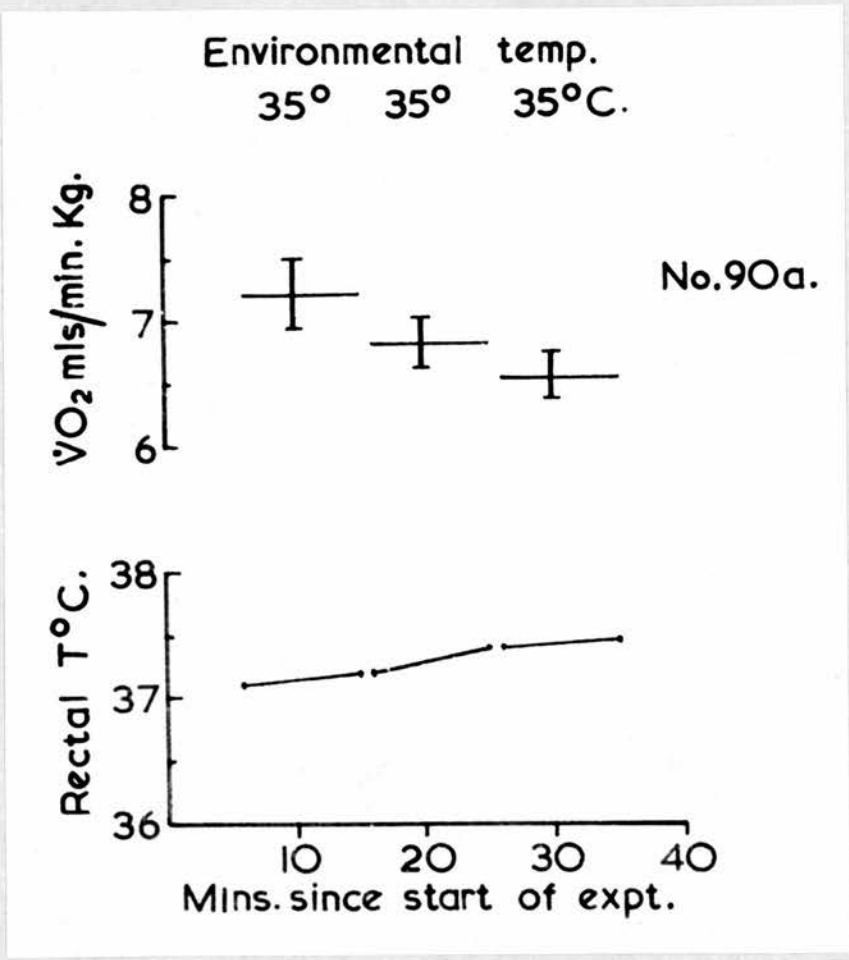


Fig. 27d

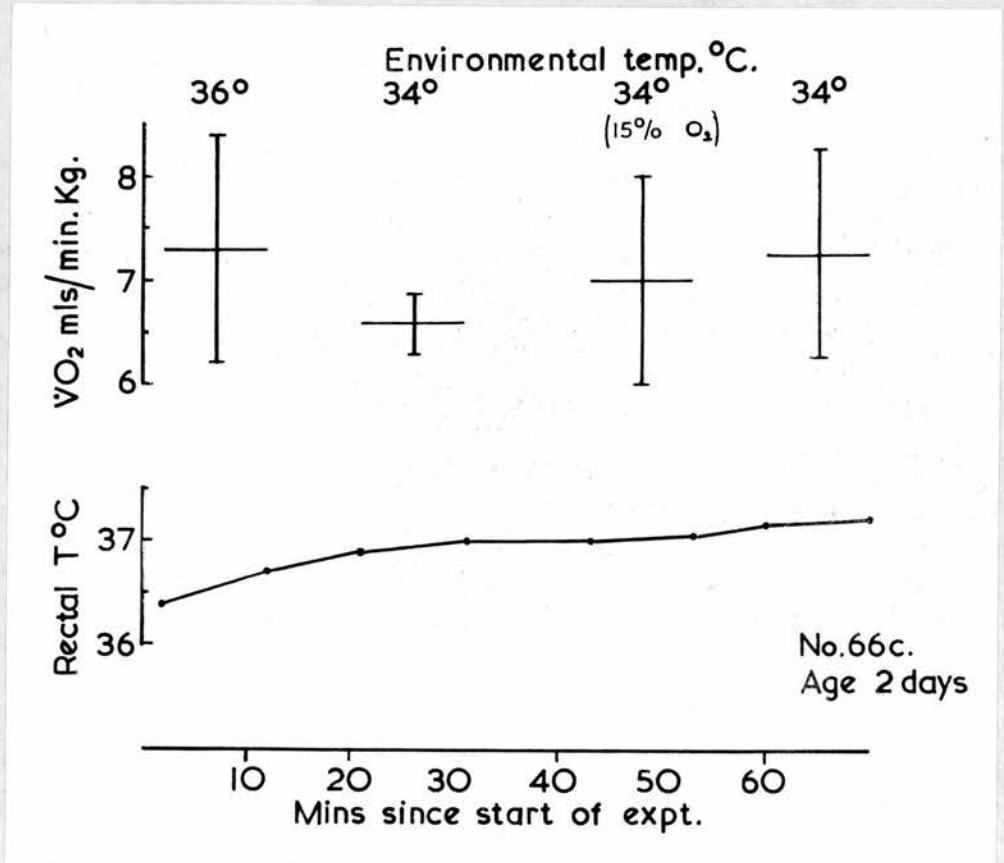


Fig. 27e

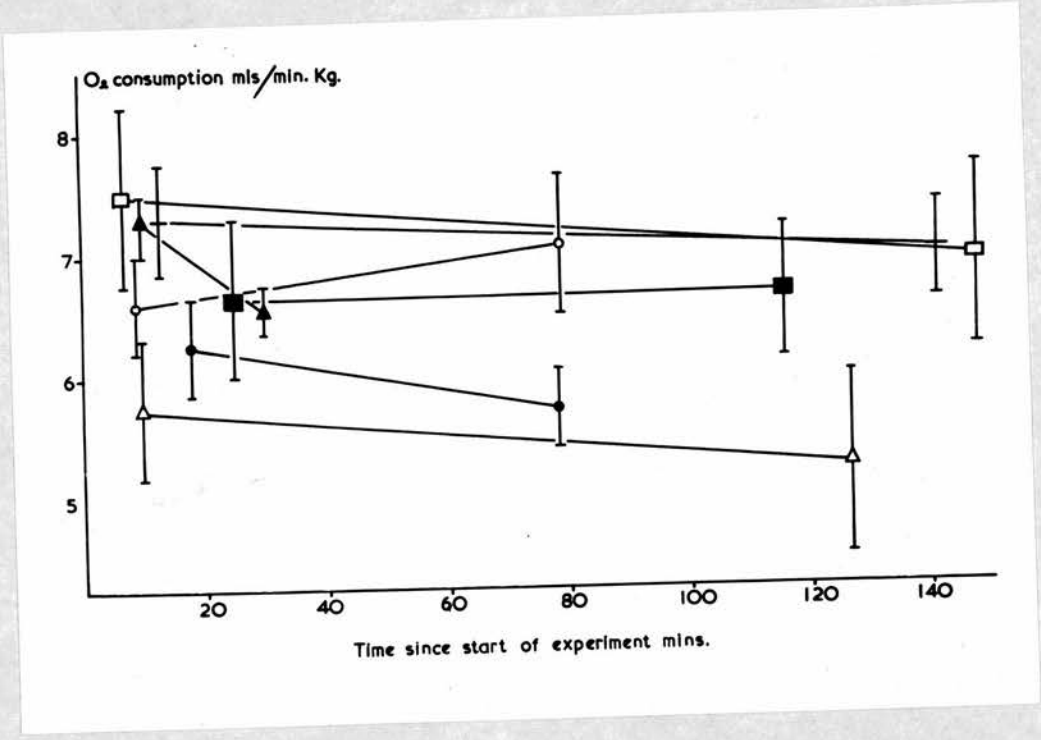


Fig. 28. Measurements of oxygen consumption over 10 minute periods (mean ——— , and 95% confidence limits of mean ⊤⊥) during different experiments, and time since start of experiment. Each experiment began 20–30 mins. after a feed.

Results (cont'd).

measurements of oxygen consumption at various times after feeds, the first measurements were taken about 20-30 mins. after the end of feeds. This was the approximate length of time taken to move the baby from the ward, prepare it, and start the first reading. It was thought that these observations were made sufficiently soon after feeding to represent a control period. Fig. 28 demonstrates that the measurements of oxygen consumption 45-140 mins. after the control measurement were not significantly different; the babies were subjected to various stresses of hypoxia and low rectal temperatures between these two observations and it is possible these stresses might act to diminish differences.

However similar results were obtained by Oliver and Karlberg (1963) who performed repeated measurements of oxygen consumption after feeding breast milk by naso-oesophageal tube to 5 normal infants in constant environmental conditions. They found that there was no sustained effect attributable to the increased activity during feeding nor was a specific dynamic effect noted. Similarly Lee and Iliff (1956) concluded that the specific dynamic effect produced smaller errors than those caused by restlessness and hunger, and Hill and Rahimtulla (1965) concluded that it made no difference to the basal metabolic rate whether the last feed had been taken ½ or 3 hours previously.

The finding that food has only a small or no effect on the basal metabolic rate may well be due to the fact that an infant is still digesting the last feed when he receives his next.

Results (cont'd).

Reproducibility of Measurements of Basal Metabolic Rate and the Effect of Activity.

An attempt was made to assess the reproducibility of measurements of basal metabolic rate and to estimate the amount of random variation to be expected. The major known causes of change in oxygen consumption in a particular normal infant at a given age are environmental temperature, and activity. An investigation was performed to see if the effects of activity on oxygen consumption were predictable.

Environmental Temperature.

Changes due to this factor were eliminated so far as possible by considering only quiet babies at the same or slightly different environmental temperature within the neutral temperature range, where by definition, changes in environmental temperatures are unassociated with changes in oxygen consumption. In naked babies the lower limit of the neutral temperature range, i.e. the critical temperature, was assumed to be that previously suggested, (34-37°C on the day of birth, about 34°C on the 2nd to 6th and 7th day, and 30-33°C on the 7th to 9th days). Some of our subjects were clothed and for these a critical temperature has not yet been defined in this apparatus. However we only accepted metabolic rates as basal (for clothed babies) if the oxygen consumption was in the range basal metabolic rate $\pm$ 2 standard deviations of Hill and Rahimtulla (1965) while the baby was inactive, in a warm environment.

Activity.

Recent studies have shown that even during sleep there may be significant changes in oxygen consumption of

Results (cont'd).

about 15% (Scopes, 1966). It is therefore not surprising to find changes in quiet babies who are awake. Only quiet infants who were virtually inactive were considered although they could be awake or asleep. A quiet state in babies is difficult to define and in fact when the babies who are asleep or sleepy are carefully observed they often show whole body movements or movements of a single limb which raise the average activity rating, on our scale over a 10 minute period to values slightly greater than 1.0.

Aserinsky and Kleitman (1955), Brück, Parmelee and Brück (1962a) and Goldie (1965) have described the sleep cycles of full term and premature infants. During a period of about 20 minutes there is a relatively complete cessation of eye movements and of gross bodily activity, associated with lowered pulse and respiration rates. This is followed by a phase lasting about 55 mins. of body and rapid eye movements which may persist as a "period of subwaking" or as frank wakefulness with open eyes and crying. This active phase is followed by the phase of inactivity and the cycle repeats itself until interrupted by feeding. Only quiet or inactive infants were included in this study. Crying infants were excluded from the major part of the study and they are considered only in Table 13.

In the warm (neutral temperature range) the babies usually slept but were occasionally active. In the cool however many quiet babies tended to become slightly restless (a finding noted by Day (1943) and amplified by Brück, Parmelee and Brück (1962). Scopes (1966) stated that small irregular movements were almost always associated with the metabolic response to cold.

Results (cont'd).

As it was later necessary to compare the oxygen consumption in air and 15% oxygen of babies whose activities might differ slightly in the two gases, the effect of activity on the reproducibility of results was assessed. This section attempts to show whether slight variations in activity assessed by the arbitary scale have a demonstrable effect on oxygen consumption. We gained the impression that activity gradings of 1.5 or less were not associated with significant changes in oxygen consumption. It must be emphasised that an activity of 1.1 for instance, is not much different from one of 1.0. It means only that for 2 mins. out of 10 mins. "moving arms and legs" seemed a more suitable description than "only an occasional jerk". Therefore it seems unlikely that this would produce a big increase in oxygen consumption.

To consider the reproducibility the oxygen consumption was measured in successive 10 minute periods in air at a neutral temperature as defined above. Thirty measurements of the mean oxygen consumption over a period of 10 minutes each followed by a similar measurement were obtained from 12 normal infants. The second measurement was compared with the first. Where oxygen consumption was measured in 3 successive periods, the first was compared with the second and third, and the second and third were compared with each other. All the subjects were breathing air in every period and the rectal temperature and the environmental temperature changes were minimal. The results were divided according to the amount of activity:-

1. Measurements in which the babies were inactive.
2. Measurements in which the babies were slightly active.

Results (cont'd).

Because a mixed group of measurements in which the babies were both inactive or slightly active was considered in the air and 15% oxygen experiments, the preceeding two groups are then considered together:-

3. Both the above groups combined.

1. Inactive Babies.

A group of inactive babies was first considered (Table 3). In 15 experiments, during two sets of 10 minute periods, measurements of oxygen consumption were compared. These values were obtained from 8 normal full term infants breathing air in similar conditions, in the neutral temperature range. The second measurement was compared with the first. The thermal conditions in the 2 groups were almost identical and there were only small changes in rectal and environmental temperatures. The rectal temperature showed very small but very consistent changes. The mean change was a rise of 0.2°C and in 13 cases out of 15 the rectal temperature rose. In 1 case it stayed constant and in only 1 was there a fall. These changes suggest that the babies were in a heat gaining environment in which Adamsons et al. (1965) have shown that the oxygen consumption is basal. Although they are slight, precisely similar changes occur in both the other 2 groups of babies considered in the warm, (see Active Babies, and Effect of 15% Oxygen in the Warm). The environmental changes were also very small, and the mean change in environmental temperature for both periods was a fall of 0.5°C although the mean environmental temperature for both periods was the same.

The activity was recorded as 1.0 in both the first and second periods and the interval between the beginning

TABLE 3

SUCCESSIVE MEASUREMENTS OF OXYGEN CONSUMPTION IN INACTIVE BABIES

Exp. No:	Clothing	Period No:	Age Days	1st Period Te °C	1st Period VO_2	1st Period Rectal temp. Start / Finish	1st Period Activity	2nd Period Te °C	2nd Period VO_2	2nd Period Rectal temp. Start / Finish	2nd Period Activity	Time in mins from start of Period 1 to start of Period 2	% change of Period 2 on Period 1 ±
64A	N	1 & 2	0.5	38	5.62	37.0 / 37.0	1.0	36	5.78	37.1 / 37.2	1.0	20	2.9
73B	N	1 & 2	5	32	7.58	36.4 / 36.5	1.0	34	6.00	36.4 / 36.5	1.0	25	23.6
79C	C	7 & 8	8	32	7.63	36.7 / 36.7	1.0	34	6.31	36.7 / 36.6	1.0	18	17.3
80B	N	4 & 5	13	37	7.36	36.8 / 37.1	1.0	36	6.97	37.3 / 37.5	1.0	18	5.3
80B	N	5 & 6	13	36	6.97	37.3 / 37.5	1.0	35	7.52	37.7 / 37.8	1.0	18	7.9
80B	N	6 & 7	13	35	7.52	37.7 / 37.8	1.0	36	7.10	37.8 / 37.9	1.0	18	5 .6
80B	N	7 & 8	13	36	7.10	37.8 / 37.9	1.0	36	7.25	38.0 / 38.0	1.0	15	2.1
85C	C	1 & 2	4	33	7.50	36.7 / 36.7	1.0	30	7.98	36.8 / 36.9	1.0	18	6.4
88A	C + S	1 & 2	5	34	6.64	37.1 / 37.1	1.0	30	6.80	37.1 / 37.2	1.0	15	2.4
88A	C + S	2 & 3	5	30	6.80	37.1 / 37.2	1.0	28	6.59	37.2 / 37.1	1.0	20	3.1
88B	C + S	1 & 2	6	35	7.28	37.4 / 37.4	1.0	35	6.58	37.4 / 37.5	1.0	10	9.6
90A	C + S	1 & 2	6	35	7.24	37.1 / 37.2	1.0	35	6.83	37.2 / 37.4	1.0	10	5.7
90A	C + S	6 & 3	6	35	7.24	37.1 / 37.2	1.0	35	6.55	37.4 / 37.5	1.0	20	9.5
66A	N	1 & 2	0.5	36	4.83	35.4 / 35.5	1.0	35	4.64	35.6 / 35.6	1.0	19	3.9
66A	N	1 & 3	0.5	36	4.83	35.4 / 35.5	1.0	35	4.67	35.6 / 35.6	1.0	30	3.3
		MEANS	3.9	34	6.83		1.0	34	6.50		1.0	17	- 4.35% S.D. = 8.47%

Mean rise in Rectal temperature 0.2°C
Mean change in Te = fall of 0.5°C

Clothing N = Naked
C = Clothed, without a sheet as in Table 11A
C + S = Clothed, with a sheet as in Table 12A

Oxygen concentration mls/min. Kg.
Rectal Temperature °C

Results (cont'd).

of the periods varied from 15 to 25 minutes mean 17 minutes.

The mean oxygen consumption in the first and second measurements is shown in Table 4. A t test indicates that there is no difference between the means.

The mean change in oxygen consumption was a fall in period 2, of 0.33 mls/min per Kg. (4.35%, S.D. 8.47%), and this was not significantly different from zero (P less than 0.1, P greater than 0.05).

2. Slightly Active Babies.

A total of 15 pairs of 10 minute periods of oxygen consumption measurements were obtained from the data (Table 5). In every case the baby was breathing air and was exposed to a temperature within the neutral range. In each measurement the mean activity was between 1.0 to 1.5 units. The mean time between the beginnings of the periods was 18 minutes and the rectal temperature showed consistent changes similar to those in the inactive babies:- a rise of 0.35°C (maximum change 0.6°C).

The mean change in environmental temperature, within the neutral range, was a fall of 1.5°C although the difference between the means was only 1°C. The mean oxygen consumptions in the first and second measurements are shown in Table 6. A t test showed that the mean oxygen consumptions were not significantly different (P greater than 0.1). This slight rise in oxygen consumption coincided with a slight increase in activity from the mean of 1.09 units in the first period to a mean of 1.15 units in the second period.

The mean change between period 1 and period 2 was a rise of 0.33 mls/min. Kg. (S.D. 0.61) and this was not significantly different from zero (0.1 greater than P greater than 0.05).

TABLE 4

INACTIVE BABIES: REPEATED MEASUREMENTS OF OXYGEN CONSUMPTION IN TWO 10 MIN. PERIODS, ACTIVITY GRADING 1.0 IN EACH.

	Oxygen consumption in mls/min. Kg.			
	Mean	1 S.D.	1 S.E.M.	Mean activity
Period 1 n = 15	6.83	0.97	0.25	1.0
Period 2 n = 15	6.50	0.97	0.25	1.0

The difference between the means was tested and P>0.1 (t = 1.3, D.F. = 28)

Mean difference in successive readings. (mls/min.Kg)	Mean	1 S.D.	1 S.E.M.	Probability of difference from zero arising by chance
Period 1 - Period 2 n = 15	0.323	0.64	0.17	0.1>P>0.05 (t = 1.95)
Mean of the change in successive readings expressed as a % of the first reading. (n = 15)	4.35%	8.47%	2.19%	0.1>P>0.05, t = 1.99, D.F.14
				At 14 degrees of freedom and P = 0.05, t = 2.145

Data of Table 3

TABLE 5

SUCCESSIVE MEASUREMENTS OF OXYGEN CONSUMPTION IN SLIGHTLY ACTIVE BABIES

Exp. No:	Clothing	Period No:	Age Days	1st Period Te °C	1st Period VO_2	1st Period Rectal temp. Start / Finish	1st Period Activity	2nd Period Te °C	2nd Period VO_2	2nd Period Rectal temp. Start / Finish	2nd Period Activity	Time in mins from start of Period 1 to start of Period 2	% change of Period 2 on Period 1 ±
38A	N	2 & 3	0.1	38	4.47	35.4 / 35.6	1.0	36	5.31	35.8 / 36.0	1.2	15	18.8
38E	N	1 & 2	10	34	7.20	37.0 / 37.1	1.1	32	7.14	37.1 / 37.0	1.0	18	0.8
38F	N	1 & 2	11	34	8.22	37.1 / 37.2	1.1	32	9.09	37.2 / 37.2	1.1	19	10.6
60A	N	1 & 2	0.7	37	6.25	35.8 / 36.1	1.0	35	6.45	36.2 / 36.3	1.3	16	3.2
60B	N	1 & 2	1.7	36	6.93	35.8 / 36.1	1.1	34	7.17	36.2 / 36.3	1.2	18	3.5
60B	N	2 & 3	1.7	34	7.17	36.2 / 36.3	1.2	38	6.49	36.4 / 36.6	1.1	22	9.5
64B	N	1 & 2	1.4	38	6.33	37.0 / 37.1	1.2	36	7.48	37.3 / 37.4	1.2	22	18.2
64C	N	1 & 1b	2	38	6.61	36.9 / 37.0	1.0	36	6.70	37.2 / 37.3	1.1	15	1.4
65C	N	1 & 2	2	36	6.49	37.3 / 37.4	1.1	32	7.67	37.4 / 37.4	1.2	31	18.2
66B	N	1 & 2	1.4	36	6.22	36.4 / 36.4	1.0	34	6.25	36.4 / 36.5	1.1	19	0.5
66C	N	1 & 2	2	36	7.31	36.4 / 36.7	1.1	34	6.59	36.9 / 37.0	1.0	17	9.8
79B	N	5 & 6	6	34	7.27	35.8 / 36.0	1.0	32	7.98	36.0 / 36.0	1.1	15	9.8
94A	N	1 & 2	8	37	8.79	36.7 / 36.8	1.1	37	8.82	36.8 / 37.0	1.3	8	0.3
94B	N	2 & 3	9	36	7.55	- / -	1.0	36	7.58	- / -	1.3	10	0.4
94B	N	3 & 4	9	36	7.58	- / -	1.3	36	8.61	- / -	1.1	10	13.6
		MEANS [n=15]	2.9	36	6.96		1.09	35	7.24		1.15	18	+ 5.23 S.D. 9.30

Mean rise in Rectal Temperature 0.35°C
Mean change in Te = rise of 1.5° C

N = naked.

Oxygen concentration mls/min. Kg.
Rectal Temperature °C

TABLE 6

SLIGHTLY ACTIVE BABIES: REPEATED MEASUREMENTS OF OXYGEN CONSUMPTION IN MLS/MIN.KG. IN TWO 10 MIN. PERIODS.

	Oxygen consumption in mls/min. Kg.			
	Mean	1 S.D.	1 S.E.M.	Mean activity
Period 1 n = 15	6.96	0.97	0.25	1.09
Period 2 n = 15	7.29	1.15	0.30	1.15

The difference between the means was tested: P>0.1, t = 1.4, D.F. = 28

	Mean	1 S.D.	1 S.E.M.	Probability of difference from zero arising by chance (paired comparison test)
Mean difference in successive readings. (mls/min.Kg) Period 1 - Period 2 n = 15	- 0.329	0.61	0.16	0.1>P>0.05 t=2.088, D.F.14
Mean of the change in successive readings (Period 1 - Period 2) expressed as a % of the first reading. (n = 15)	- 5.23	9.30	2.40	0.05>P>0.02 (t=2.177, D.F.14) At 14 degrees of freedom and P = 0.05, t = 2.145

Data of Table 5

Results (cont'd).

If the data is transformed so that the difference between period 1 and period 2 is expressed as a % of the oxygen consumption in period 1 the absolute difference is related to the initial oxygen consumption; a given change in an infant with a small oxygen consumption is more likely to be important than the same change in a baby with a larger oxygen consumption. With this method the difference from zero is just above the conventional, 5% level (0.05 greater than P greater than 0.02).

Despite the statistical significance of this result the small size of the difference, 5%, would not be expected to obscure the 17% change in oxygen consumption found by Cross et al. (1958), and Oliver and Karlberg (1964), and it seems unlikely to be of practical importance. The slight mean rise in oxygen consumption coincided with a rise in activity of 0.07 units, which is so slight that it could not be measured in the individual baby. This amount of mean change in activity is less than that found in the 15% oxygen experiments and it suggests that lesser changes can be safely discounted as a cause of changing oxygen consumption.

Comparison of Active and Inactive Groups. The mean oxygen consumptions in the active and inactive groups are shown in Table 7. The higher mean oxygen consumption in the active babies is not significant statistically (0.1 greater than P greater than 0.05). The two groups are not homogenous for age and this, and individual variations in the basal metabolic rate confirm the statistical suggestion that the differences are not of practical significance.

TABLE 7

COMPARISON OF ACTIVE AND INACTIVE GROUPS

Subject	Mean activity	Mean oxygen consumption mls/min.Kg.	1 S.D.	1 S.E.M.	n
Inactive babies (Periods 1 and 2 combined)	1.0	6.67	0.95	0.17	30
Active babies (Periods 1 and 2 combined)	1.12	7.12	1.03	0.19	30

Probability of difference arising by chance: $t = 1.77$, D.F.58; $0.1 > P > 0.05$

Results (cont'd).

3. Inactive and Slightly Active Babies Combined.

As a mixed group of quiet and active babies is considered in the 15% oxygen experiments the group as a whole will be considered (Table 8). Table 8 shows that a high degree of reproducibility has been obtained. The mean oxygen consumptions of both periods are the same and the mean difference between the oxygen consumptions in period 1 and period 2, whether expressed in raw figures or as a percentage of the oxygen consumption in period 1 is very small and is not significantly different from zero.

The degree of variation is of the same order as that found by Cross et al. (1957), (Table 1). In a similar series of 11 pairs of measurements of oxygen consumption in air these investigators found that the mean percentage change in oxygen consumption was a fall of 0.05% with a standard deviation of 7.1%. Oliver and Karlberg (1963) have also found a somewhat similar degree of variation. They state "For two 10 minute periods, 20-30 minutes apart, 95% of second values should be within $\pm$ 7.6% above or below the initial value." Adamsons et al. (1965), and Brück (1961), among recent authors on oxygen consumption in the newborn infant, do not describe the degree of reproducibility of their experiments.

Sensitivity of method.

The extent of variability in this group of babies in the warm having been defined, the next question which arises is whether the method is sufficiently sensitive to detect a fall in oxygen consumption in 15% oxygen of the same order as that found by the previous workers in this field. The experiments were done to repeat the work of

TABLE 8

OXYGEN CONSUMPTION MEASUREMENTS IN TWO 10 MIN. PERIODS, PERIOD 1 AND PERIOD 2, IN A GROUP OF QUIET BABIES.
(TABLES 3 AND 5 COMBINED)

	Oxygen consumption in mls/min. kg.		
	Mean	1 S.D.	1 S.E.M.
Period 1 n = 30	6.90	0.96	0.18
Period 2 n = 30	6.90	1.07	0.20

The difference between the means was tested: t = 0, D.F. = 58, P>0.99

Mean of the difference in successive readings. (mls/min.Kg)	Mean	1 S.D.	1 S.E.M.	Probability of difference from zero arising by chance
Period 1 - Period 2 n = 30	- 0.005	0.71	0.13	P>0.9, D.F.28, t<1
Mean of change in successive readings (Period 1 - Period 2) expressed as a % of the first reading n = 30	- 0.8%	10%	1.8	P>0.5, D.F.28, t = 0.6

Results (cont'd).

Cross et al. (1958), who found that the mean fall in oxygen consumption in 15% oxygen was 17%. It is interesting to calculate how many paired measurements with a mean lowering of oxygen consumption of 17% would be needed to give a difference statistically significant at the 1% level. It can be calculated (see Appendix 1) that only six such results would be needed and in the warm at least the experimental method is easily sensitive enough to detect an average fall of 17%.

It is concluded that changes of activity within the range considered (less than 1.5 units) have no important effect on oxygen consumption.

This amount of activity appears to correspond to that accepted by Oliver and Karlberg (1963). They state that measurements were considered valid only when the infants were asleep and showed either 0, or 0 with scattered + activity (0: infant asleep not moving, +: infant asleep and moving one extremity or awake and quiet.) On the other hand the infants studied by Cross et al. (1958) were asleep.

In more active babies, activity greater than 1.5 arbitrary units, there were very variable changes in oxygen consumption and if the activity grading reached 3 in a 2 minute period the 10 minute period in which this occurred was rejected. Since 3 is the lowest activity grading associated with crying no baby recorded as crying for a 2 minute period was included.

Reproducibility in a Cool Environment.

In a later section on page 113 the reproducibility in the cool, in quiet babies, is found to be the same as in the warm environment.

Results (cont'd).

EXPERIMENTS WITH 15% OXYGEN

Design of Experiments.

These investigations were performed to repeat the work of Cross, Tizard and Trythall (1958) and Oliver and Karlberg (1963). Our experimental design was arranged to reproduce the one followed in both the other papers as closely as possible. Thus while the thermal conditions were held constant, oxygen consumption was measured in air (period 1) then while breathing 15% oxygen (period 2). The earlier experimental design was extended by measuring oxygen consumption in air again after 15% O_2 providing there was sufficient time (period 3). Comparison between period 1 and period 2 indicates the effect of hypoxia; comparison between period 1 and period 3 indicates the amount of random variation to be expected in identical thermal conditions 20-30 minutes apart and would incidentally show any after effects of 15% oxygen. Comparison between period 2 and period 3 in effect varies the order of exposure to 15% oxygen.

The response of many newborn animals to hypoxia in thermally neutral conditions, called "in the warm" for brevity, is known to differ (Hill, 1959) from that in the thermal conditions below the critical point, "in the cool". Babies were studied in both environments; initially the babies were studied while naked but since the babies were clothed in the experiments of Cross et al. (1958) and Oliver and Karlberg (1963), it became necessary to consider whether clothing had any effect.

In the neutral thermal zone ("in the warm"), oxygen consumption is no longer lowered by increasing the

Results (cont'd).

environmental temperature and the oxygen consumption was always measured at higher environmental temperatures to see that it was not significantly lower than that at the temperature chosen. Before experiments in the cool, oxygen consumption was first measured in the warm to establish a value for basal metabolic rate so that the metabolic response to cold for each individual baby would be known.

No experiments in the warm needed to be rejected because of high activity, but if in the cool the activity exceeded 1.5 in any of the periods used for comparison, the results are considered later, page 113. Changes in activity between 1.0 and 1.5 units are within the limits described in the previous section.

Investigations were done on 21 full term normal infants with ages ranging from 6 hours to 11 days (mean 3.7 days) and whose weights varied from 2.60 kg. to 4.20 Kg. (mean 3.34 Kg.). Infants were exposed to 15% oxygen in 94 10 minute periods.

Results (cont'd).

EFFECTS OF 15% OXYGEN IN THE WARM.

The results are shown in Tables 9a and 9b and graphically in Figs. 29, 30 and 31. Six babies were examined and all were naked except the last two in the Table; the first three were not examined by the author. All the measurements of oxygen consumption both in infants breathing air and in infants breathing 15% oxygen were within the range B.M.R. $\pm$ 2 standard deviations of Hill and Rahimtulla (1965). Fig. 31 shows that the results in all three periods are normally distributed.

The results of Tables 9a and 9b (and of Tables 10, 11, 12, 13) were evaluated statistically by both t tests on mean values, and paired comparison tests. The mean oxygen consumption in period 1 was compared by t tests with that in period 2, and that in period 3. The mean value in period 2 was similarly compared with that in period 3. In paired comparison tests the mean change in oxygen consumption between period 1 and period 2 was calculated and the significance of its difference from zero was tested. The mean change between period 2 and 3 and period 1 and 3 was tested similarly.

The results show that there was no significant change in oxygen consumption (P greater than 0.1).

This confirms the results of Oliver and Karlberg (1963) in the thermo-neutral environment, and is in accord with the work of Hill (1959) in kittens.

TABLE 9A

OXYGEN CONSUMPTION OF NAKED BABIES IN THE WARM WHEN BREATHING AIR OR 15% OXYGEN

Exp. No.	Age in Days	Wt. kg.	Sex	Env. Temp.	Period I : Air				Period II: 15% O_2				Period III : Air				% change	
					Activity	O_2 cons. ml/min kg.	1 SD	1 SE	Activity	O_2 cons. ml/min kg.	1 SD	1 SE	% change II on I	% O_2	Activity	O_2 cons. ml/min kg.	1 SD	1 SE	III on I	III on II
4A	4	3.68	F	35	1.0	6.80	0.56	0.12	1.3	6.80	0.88	0.22	0	14.0						
4C	11	3.92	F	30	1.0	7.11	0.89	0.22	1.3	7.27	2.09	0.52	+ 2	14.6	1.0	7.90	0.81	0.20	+11	+ 9
4D	11	3.92	F	35	1.0	7.07	0.76	0.20	1.5	7.50	1.58	0.40	+ 6	15.0						
5A	2	2.76	F	35	1.0	6.70	3.08	0.76	1.0	6.50	1.40	0.34	- 3	15.0	1.3	7.10	2.38	0.60	+ 6	+ 9
5C	4	2.82	F	35	1.3	7.20	1.28	0.32	1.3	6.60	1.38	0.34	- 8	15.0	1.3	7.30	2.34	0.58	+ 1	+11
5D	4	2.82	F	30	1.3	7.50	2.24	0.56	1.3	6.40	1.87	0.47	-15	15.0						
5F	9	3.02	F	35	1.0	7.30	0.98	0.24	1.0	7.10	1.62	0.40	- 3	15.0	1.3	7.50	1.18	0.30	+ 3	+ 6
6A	17 hrs	3.16	F	35	1.0	5.75	1.12	0.26	1.0	6.19	0.88	0.20	+ 5	15.0	1.0	5.45	0.90	0.20	- 5	-12
6D	3	3.05	F	35	1.0	6.14	1.32	0.30	1.0	6.20	1.66	0.38	+ 2	15.0	1.0	6.69	1.32	0.38	+ 5	+ 8
66A	8 hrs	3.37	M	35	1.0	4.64	0.50	0.12	1.0	4.75	1.42	0.32	+ 4	14.5	1.0	4.99	1.78	0.40	+ 9	+ 5
66B	32 hrs	3.22	M	34	1.1	6.25	2.46	0.54	1.0	5.74	1.46	0.32	- 9	14.5	1.0	6.36	2.20	0.50	+ 2	+11
66C	2	3.17	M	34	1.0	6.59	0.60	0.14	1.1	7.03	2.18	0.48	+ 6	15.5	1.0	7.23	2.24	0.50	+ 9	+ 3
66D	4	3.36	M	34	1.0	6.49	0.58	0.12	1.1	6.65	2.10	0.48	+ 3	14.5	1.0	7.37	2.44	0.54	+14	+11
66E	7	3.60	M	34	1.1	8.43	1.38	0.30	1.0	7.21	1.08	0.24	-14	14.5	1.0	7.79	1.66	0.36	- 7	+ 8
69A	6 hrs	4.23	M	34	1.0	5.64	2.09	0.47	1.1	4.90	0.90	0.20	-12	14.8						
85A*	2	2.60	M	32	1.0	7.60	1.68	0.38	1.0	8.12	1.90	0.43	+ 7	15.0	1.0	7.00	2.09	0.47	- 8	-14
85C*	4	2.61	M	30	1.0	7.98	0.70	0.16	1.0	7.22	1.21	0.27	- 9	16.0	1.0	7.39	1.56	0.35	- 7	+ 2
Mean	4.0 days	3.25		33.6	1.04	6.78 (n=17)	0.88	0.21	1.11	6.60 (n=17)	0.87	0.21	-2.2	14.9	1.07	6.93 (n=13)	0.87	0.24	+2.5	+4.4

* Dressed in vest, nightgown, and diaper, as in Table 11.

TABLE 9B

STATISTICAL TESTS OF SIGNIFICANCE ON TABLE 9A

Subject	Mean mls/min per Kg	S.D.	Significance of difference between means	Statistical data
Oxygen consumption in Period 1 AIR	6.78	0.88)	0.6>P>0.5 (t = 0.60)	At 32 degrees of freedom P = 0.6 t = 0.53 P = 0.5 t = 0.68
Oxygen consumption in Period 2 15% O_2	6.60	0.87)		
Oxygen consumption in Period 2 15% O_2	6.60	0.87)	0.4>P>0.3 (t = 1.01)	At 28 degrees of freedom P = 0.3 t = 1.06 P = 0.4 t = 0.86
Oxygen consumption in Period 3 AIR	6.93	0.87)		
Oxygen consumption in Period 1 AIR	6.78	0.88)	0.7>P>0.6 (t = 0.48)	At 28 degrees of freedom P = 0.7 t = 0.39 P = 0.6 t = 0.53
Oxygen consumption in Period 3 AIR	6.93	0.87)		

Subject	Mean %	S.D.	Significance of difference from zero	
% change of Period 2 on Period 1, i.e. oxygen consumption in Period 2 -oxygen consumption in Period 1 as a percentage of that in Period 1	-2.2	7.4	0.3>P>0.2 (t = 1.2)	At 12 degrees of freedom P = 0.2 t = 1.36 P = 0.3 t = 1.08
% change of Period 3 on Period 2	+4.4	8.3	0.1>P>0.05 (t = 1.92)	At 12 degrees of f'dr P = 0.1 t = 1.78 P = 0.05 t = 2.18
% change of Period 3 on Period 1	+2.5	7.4	0.3>P>0.2 (t = 1.24)	At 12 degrees of freedom P = 0.3 t = 1.08 P = 0.2 t = 1.36

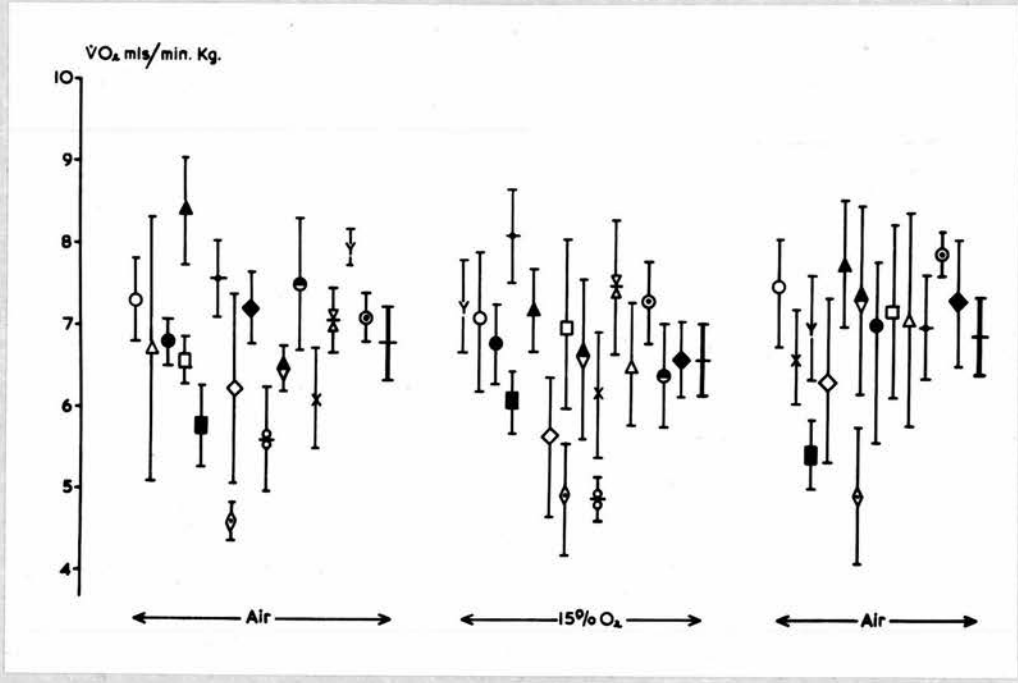


Fig. 29. Oxygen consumption ($\dot{V}O_2$) in air and 15% oxygen and air in babies in a warm environment.

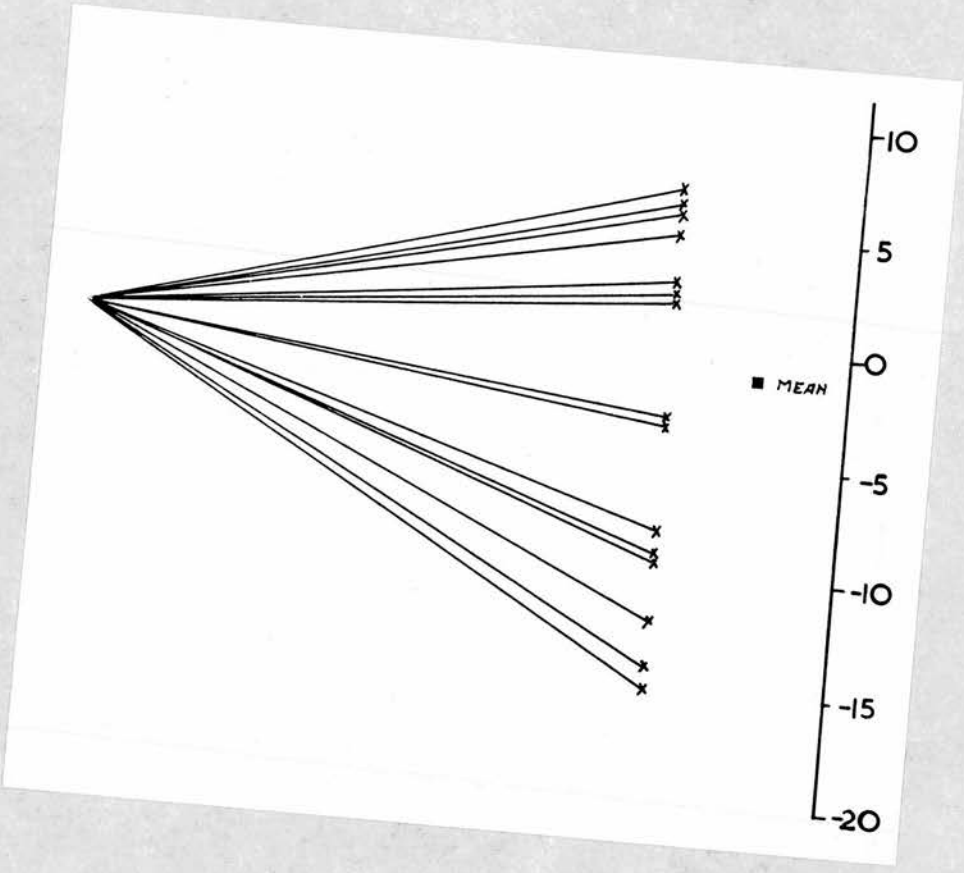


Fig. 30. Percentage changes in oxygen consumption in infants in a warm environment when breathing 15% oxygen after air. The source of the lines indicates the values in air (taken as zero), and x the percentage change on breathing 15% oxygen referred to the scale.

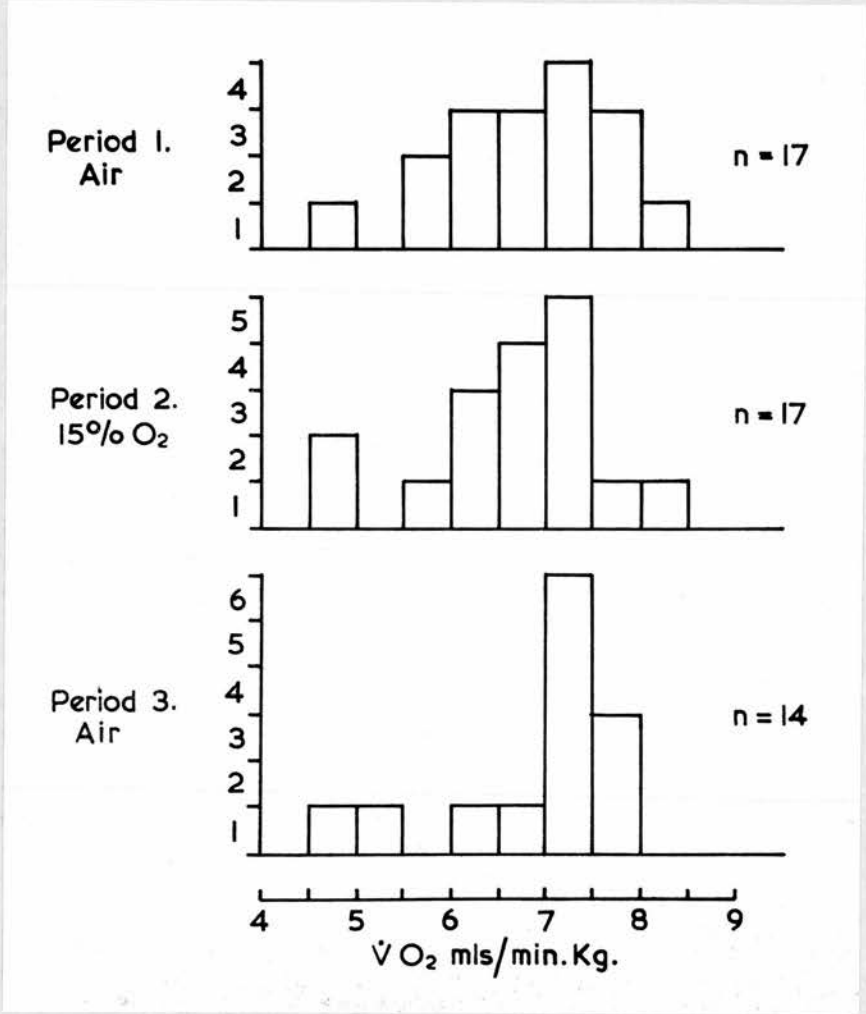


Fig. 31. Frequency distribution of measurements of oxygen consumption ($\dot{V}O_2$) in air (Period 1), followed by 15% oxygen (Period 2), and air again (Period 3). All measurements were in a warm environment.

Results (cont'd).

THE EFFECTS OF 15% OXYGEN IN THE COOL.

Naked Babies.

As in earlier work with this apparatus babies were first examined naked apart from a thin nappy and the results of 10 measurements of oxygen consumption from 6 babies first in air, and then in 15% oxygen and in some cases in air again are shown in Tables 10a and 10b and in Figs. 32, 33, and 34. The preceeding basal metabolic rates and the % increase above them are also shown. In No. 75A the same basal metabolic rates were used at 17 hours and 2 days. The first two infants were not examined by the author. Often the oxygen consumption was measured more than once in air and 15% oxygen, and some selection of the results was necessary. If there was more than one result in 15% oxygen the lowest was always used provided it was within the activity limits described; if there was more than one result in air, the period with a value for activity nearest to that in 15% oxygen was chosen. If the activity was the same in both the preceeding periods in air the last period was used. All except three of the values for oxygen consumption in air exceed the range containing 98% of the values for basal metabolic rates of Hill and Rahimtulla (1965).

Fig. 34 shows that the values for oxygen consumption were normally distributed. Again the mean oxygen consumption in periods 1, 2 and 3 were compared in pairs by a t test; and again the means of the changes in oxygen consumption between each of the 3 periods expressed as percentages were tested to examine if they were significantly different from zero. The results show that there was no significant change in oxygen consumption when the subjects breathed 15% oxygen.

TABLE 10A

OXYGEN CONSUMPTION OF NAKED BABIES IN THE COOL WHEN BREATHING AIR OR 15% OXYGEN

Exp. No.	Age	Wt (kg)	Sex	Basal O_2 cons. ml/min kg	Env. Temp.	Period I : Air					Period II : 15% O_2						Period III : Air					
						Activity	O_2 Cons. ml/min kg	% inc. above B.M.R.	1 SD	1 SE	Activity	O_2 Cons. ml/min kg	1 SD	1 SE	% Change II on I	% O_2	Activity	O_2 Cons. ml/min kg	1 SD	1 SE	% Change III on I	% Change III on II
6B	21 hrs	3.16	F	5.6	30	1.0	9.49	68	1.41	0.33	1.0	8.06	0.81	0.18	-15	15.0	1.4	10.15	2.02	0.45	+ 7	+26
18B	4 days	3.83	F	5.9	26	1.4	10.76	82	1.99	0.44	1.2	9.05	1.68	0.38	-16	14.8	1.4	10.25	2.51	0.56	- 5	+13
66B	32 hrs	3.22	M	6.2	26	1.1	10.40	68	2.88	0.64	1.0	11.73	2.78	0.62	+13	14.8	1.0	11.33	2.80	0.63	+ 9	- 3.5
66B	32 hrs	3.22	M	6.2	20	1.3	13.08	111	2.86	0.64	1.2	13.03	1.67	0.37	0	14.8						
66C	2 days	3.17	M	6.6	24	1.2	10.83	64	3.02	0.67	1.4	14.00	3.03	0.68	+29	14.6						
69C	4 days	4.17	M	6.6	26	1.5	9.22	40	2.14	0.48	1.0	9.31	1.23	0.28	+ 1	15.4						
73B	5 days	3.35	F	6.0	32	1.0	8.04	34	1.12	0.25	1.0	6.63	0.68	0.15	-17	15.5						
73C	6 days	3.40	F	6.9	31	1.05	8.43	22	1.46	0.32	1.0	7.68	1.18	0.26	- 9	15.0	1.0	6.53	1.10	0.25	-22	-18
75A	17 hrs	2.75	M	6.8	32	1.0	7.91	16	1.53	0.34	1.0	8.82	2.16	0.48	+12	15.2						
75B	2 days	2.65	M	6.8	31	1.2	8.87	38	1.61	0.36	1.3	8.90	2.19	0.50	0	15.3						
Mean	2.8 days (n=10)	3.29		6.36	27.8	1.17	9.70 (n=10)	54	1.59	0.50	1.11	9.72 (n=10)	2.40	0.76	- 0.2	15.0	1.20	9.56 (n=4)	2.09	1.05	- 2.8	+ 4.4

TABLE 10B

STATISTICAL TESTS OF SIGNIFICANCE ON TABLE 10A

Subject	Mean mls/min per Kg.	S.D.	Significance of difference between means	Statistical data
Oxygen consumption in Period 1 AIR	9.70	1.59)	P>0.9 (t = 0.02)	At 18 degrees of freedom P = 0.9 t = 0.13
Oxygen consumption in Period 2 15% O_2	9.72	2.40)		
Oxygen consumption in Period 2 15% O_2	9.72	2.40)	P>0.9 (t = 0.12)	At 12 degrees of freedom P = 0.9 t = 0.128
Oxygen consumption in Period 3 AIR	9.56	2.09)		
Oxygen consumption in Period 1 AIR	9.70	1.59)	0.9>P>0.8 (t = 0.14)	At 12 degrees of freedom P = 0.9 t = 0.13 P = 0.8 t = 0.26
Oxygen consumption in Period 3 AIR	9.56	2.09)		

Subject	Mean %	S.D.	Significance of difference from zero	
% change of Period 2 on Period 1, i.e. oxygen consumption in Period 2 - oxygen consumption in Period 1 as percentage of that in Period 1	- 0.2	14.9	P>0.9 (t -<0.1)	At 9 degrees of freedom P = 0.9 t = 0.13
% change of Period 3 on Period 2	- 4.4	17.2	0.7>P>0.6 (t = 0.55)	At 3 degrees of freedom P = 0.7 t = 0.42 P = 0.6 t = 0.58
% change of Period 3 on Period 1	- 2.8	17.3	0.8>P>0.7 (t = 0.3)	At 3 degrees of freedom P = 0.8 t = 0.28 P = 0.7 t = 0.42

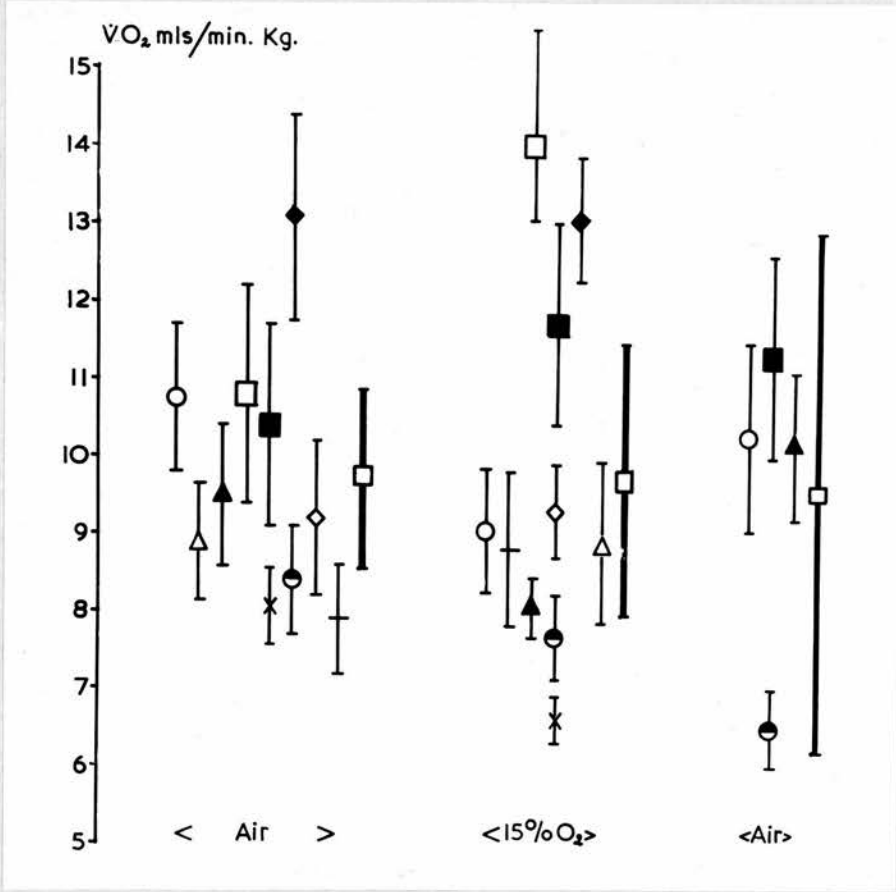


Fig. 32. Measurements of oxygen consumption ($\dot{V}O_2$) in mls/min.Kg. in naked babies in a cool environment breathing air, 15% oxygen and air. Results from the same baby at the same environmental temperature are shown by the same symbol, which indicates the mean. ⊤ 95% confidence limits of mean.

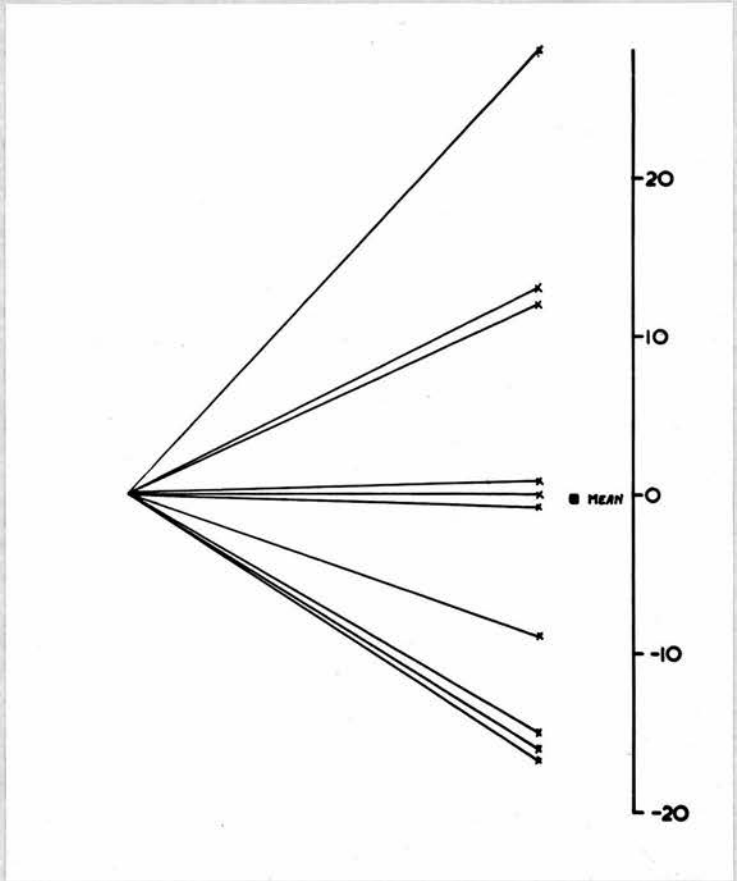


Fig. 33. Percentage changes in oxygen consumption in naked babies in a cool environment when breathing 15% oxygen. Symbols etc. as in Fig. 30.

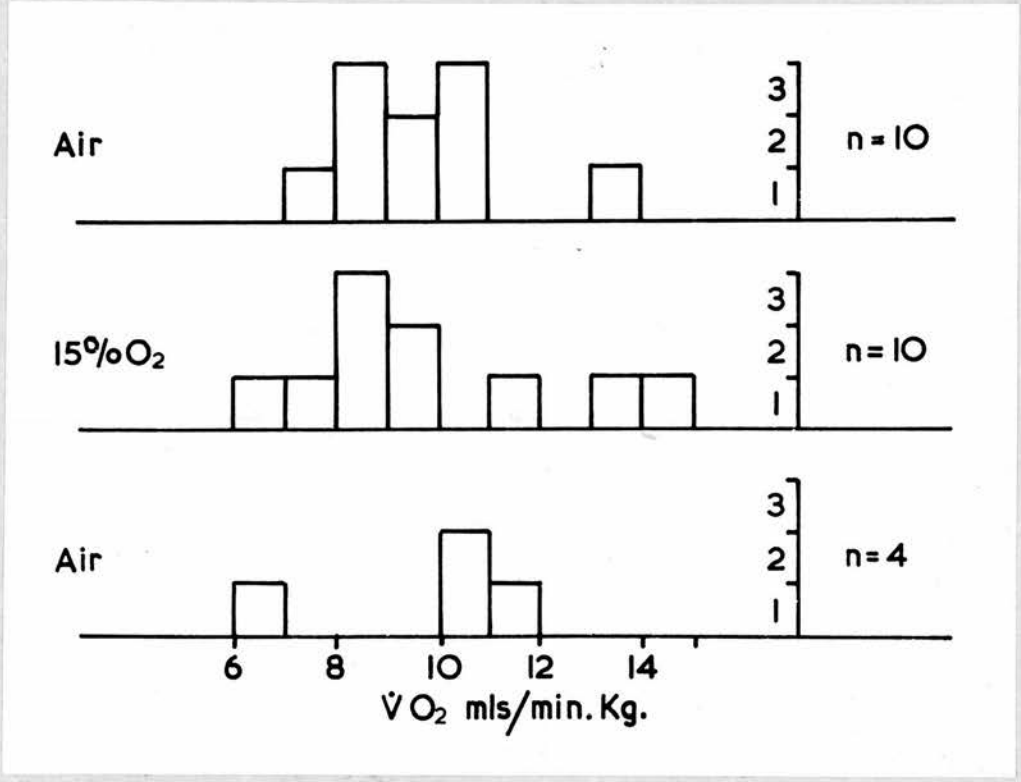


Fig. 34. Frequency distribution of measurements of oxygen consumption ($\dot{V}O_2$) in air (Period 1) followed by 15% oxygen (Period 2) followed by air (Period 3) in naked babies in the cool.

Results (cont'd).

This result was quite unexpected and various factors that could possibly cause a difference from the experimental situation of previous workers were considered in an effort to find an explanation. One major difference appeared to be in the amount of clothing. The infants studied by Cross et al. (1958) were fully clothed and their bodies and heads were surrounded by the still air of the body plethysmograph, while only the face was exposed to the stream of air or 15% oxygen. Similarly the infants studied by Oliver and Karlberg (1963) in the cool were dressed and their feet and legs were covered by a blanket; only the head and part of the chest were exposed to the air and the 15% oxygen. Two further series of experiments were performed in which the infants were clothed.

Clothed Babies.

The effects of two states of clothing were considered

A. Tables 11a and 11b and Figs. 35, 36, and 37 summarize the results in which the babies were clothed with:
Vest, Nightdress and Nappy.

B. In Tables 12a and 12b and Figs. 38, 39 and 40 another 11 experiments in which the babies were clothed as follows:
As above, with also a flannelette sheet from neck to feet.

Again the t test on the means and the tests of the significance of the mean differences from zero, applied in the same way as in Tables 9a and 9b and 10a and 10b, show that 15% oxygen had no significant effect. (P greater than 0.1 in all tests). The oxygen consumption in 15% oxygen was no different from that in air preceeding or following. In Table 11 all the oxygen consumption

TABLE 11A

OXYGEN CONSUMPTION OF PARTIALLY CLOTHED BABIES IN THE COOL WHEN BREATHING AIR OR 15% OXYGEN

Exp. No.	Age	Wt (kg)	Sex	Basal O_2 cons. ml/min kg	Env. Temp.	Period I : Air					Period II : 15% O_2						Period III : Air					
						Activity	O_2 Cons. ml/min kg	% inc. above B.M.R.	1 SD	1 SE	Activity	O_2 Cons. ml/min kg	1 SD	1 SE	% Change II on I	% O_2	Activity	O_2 Cons. ml/min kg	1 SD	1 SE	% Change III on I	% Change III on II
79C	8 days	2.87	F	6.3	26	1.1	10.45	66	1.71	0.38	1.3	8.88	1.54	0.34	-15	15.0						
82A	23½ hrs	3.25	F	6.6	26	1.1	10.64	61	1.78	0.40	1.1	10.08	1.02	0.23	- 5	15.2						
82A	24½ hrs	3.25	F	6.6	28	1.1	9.91	50	2.29	0.51	1.0	8.52	1.09	0.25	-14	15.4						
82B	3 days	3.35	F	6.6	26	1.0	8.83	34	2.61	0.58	1.2	8.72	2.05	0.46	- 1	16.0						
82C	5 days	3.45	F	6.7	26	1.1	8.66	29	1.24	0.28	1.0	8.69	0.77	0.17	0	16.1						
85A	2 days	2.60	M	7.0	28	1.2	9.20	31	3.05	0.68	1.2	9.13	1.88	0.42	- 1	15.7						
85B	3 days	2.65	M	7.0	30	1.0	9.88	41	0.75	0.17	1.1	10.87	1.44	0.32	+10	14.7	1.5	9.34	2.64	0.59	- 5	-16
85C	4 days	2.61	M	6.9	28	1.0	9.31	35	1.86	0.42	1.0	9.38	1.54	0.34	+ 1	15.5	1.1	10.08	2.15	0.48	+ 8	+ 7
87A	7 days	3.30	F	6.8	26	1.4	11.62	71	1.35	0.30	1.3	9.70	1.71	0.38	-16	15.0	1.1	10.40	1.74	0.39	-10	+ 7
87B	8 days	3.33	F	6.8	26						1.3	9.28	1.27	0.28		14.7	1.2	9.78	2.06	0.46		+ 5
Mean	4.2 days (n=10)	3.07		6.73	27	1.11	9.83 (n=9)	46	0.95	0.32	1.15	9.33 (n=10)	0.73	0.23	- 4.5	15.3	1.22	9.90 (n=4)	0.45	0.23	+ 2.3	+ 0.8

TABLE 11B

STATISTICAL TESTS OF SIGNIFICANCE ON TABLE 11A

Subject	Mean mls/min per Kg.	S.D.	Significance of difference between means	Statistical data
Oxygen consumption in Period 1 AIR	9.83	0.95)		
		)	0.3>P>0.2	At 17 degrees of freedom
Oxygen consumption in Period 2 15% O_2	9.33	0.73)	(t = 1.29)	P = 0.30 t = 1.07 P = 0.20 t = 1.33
Oxygen consumption in Period 2 15% O_2	9.33	0.73)		
		)	0.2>P>0.1	At 12 degrees of freedom
Oxygen consumption in Period 3 AIR	9.90	0.45)	(t = 1.43)	P = 0.2 t = 1.36 P = 0.1 t = 1.78
Oxygen consumption in Period 1 AIR	9.83	0.95)		
		)	0.9>P>0.8	At 11 degrees of freedom
Oxygen consumption in Period 3 AIR	9.90	0.45)	(t = 0.14)	P = 0.9 t = 0.13 P = 0.8 t = 0.26

Subject	Mean %	S.D.	Significance of difference from zero	
% change of Period 2 on Period 1, i.e. oxygen consumption in Period 2 -oxygen consumption in Period 1 as a percentage of that in Period 1	-4.5	8.8	0.2>P>0.1 (t = 1.55)	At 8 degrees of freedom P = 0.2 t = 1.40 P = 0.1 t = 1.86
% change of Period 3 on Period 2	+0.8	— [n = 3]	—	—
% change of Period 3 on Period 1	+2.3	— [n = 4]	—	—

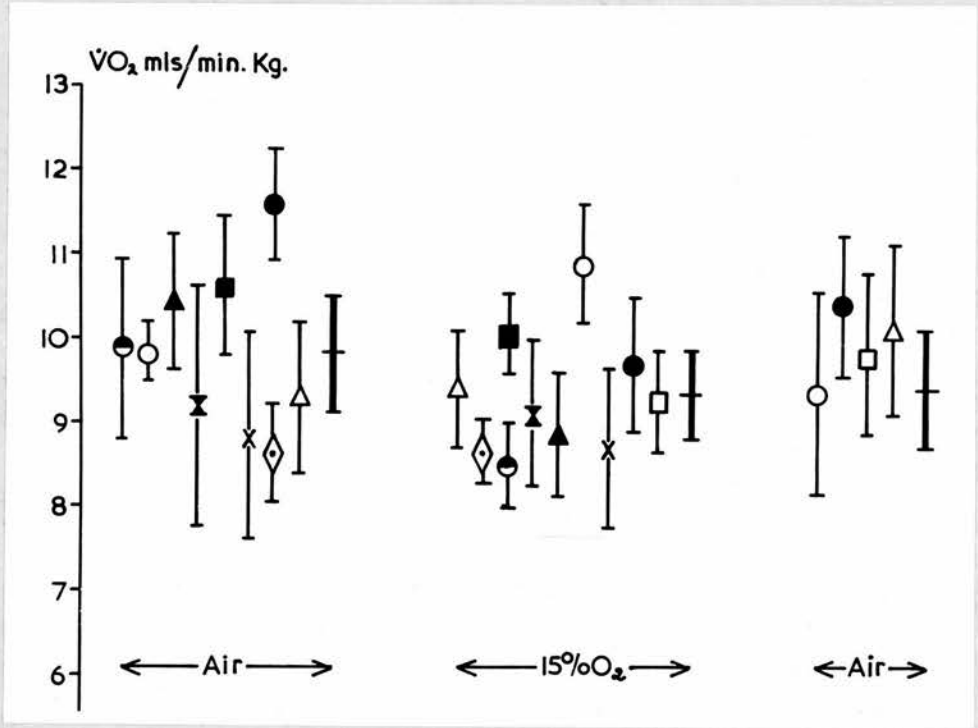


Fig. 35. Measurements of oxygen consumption ($\dot{V}O_2$) in mls/min.Kg. in babies clothed with vest, nightdress and nappy but no sheet. Babies in a cool environment breathing air, 15% oxygen then air. Results from the same baby at the same environmental temperature are shown by the same symbol which indicates the mean, and $\overset{\top}{\underset{\perp}{|}}$ indicates the standard error of the mean.

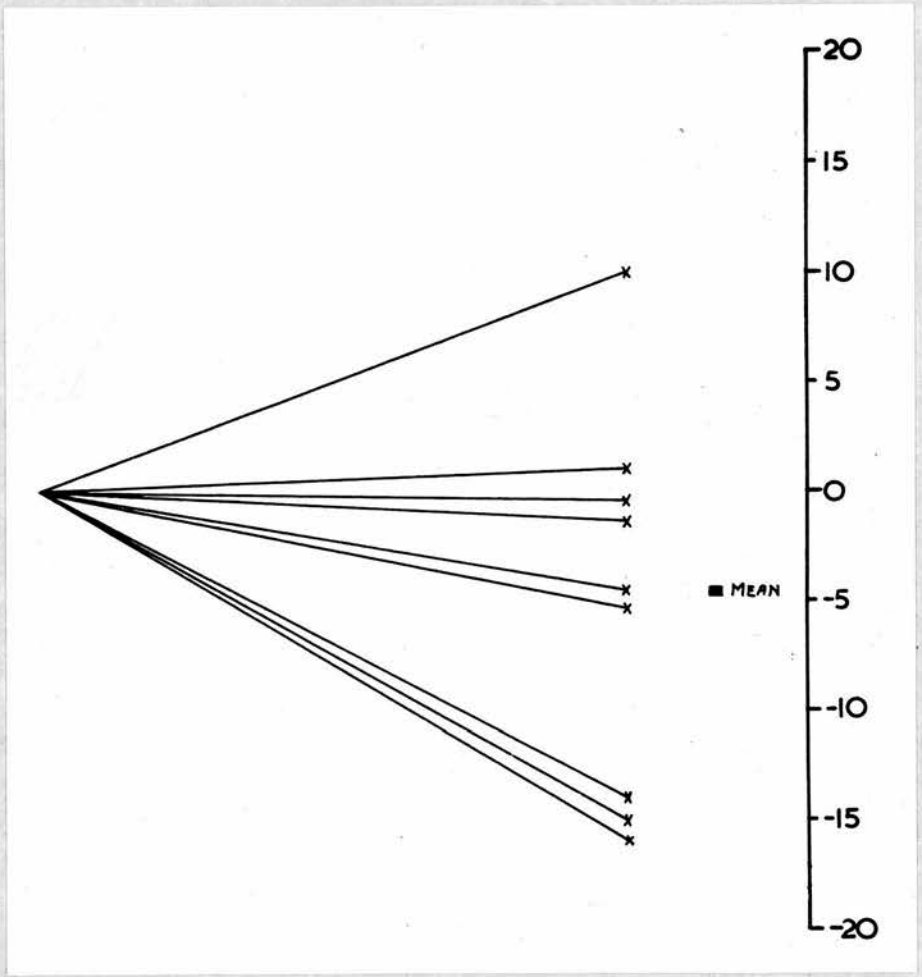


Fig. 36. Percentage changes in oxygen consumption on breathing 15% oxygen. Babies in a cool environment, clothed as in Fig. 35. Symbols as in Fig.30.

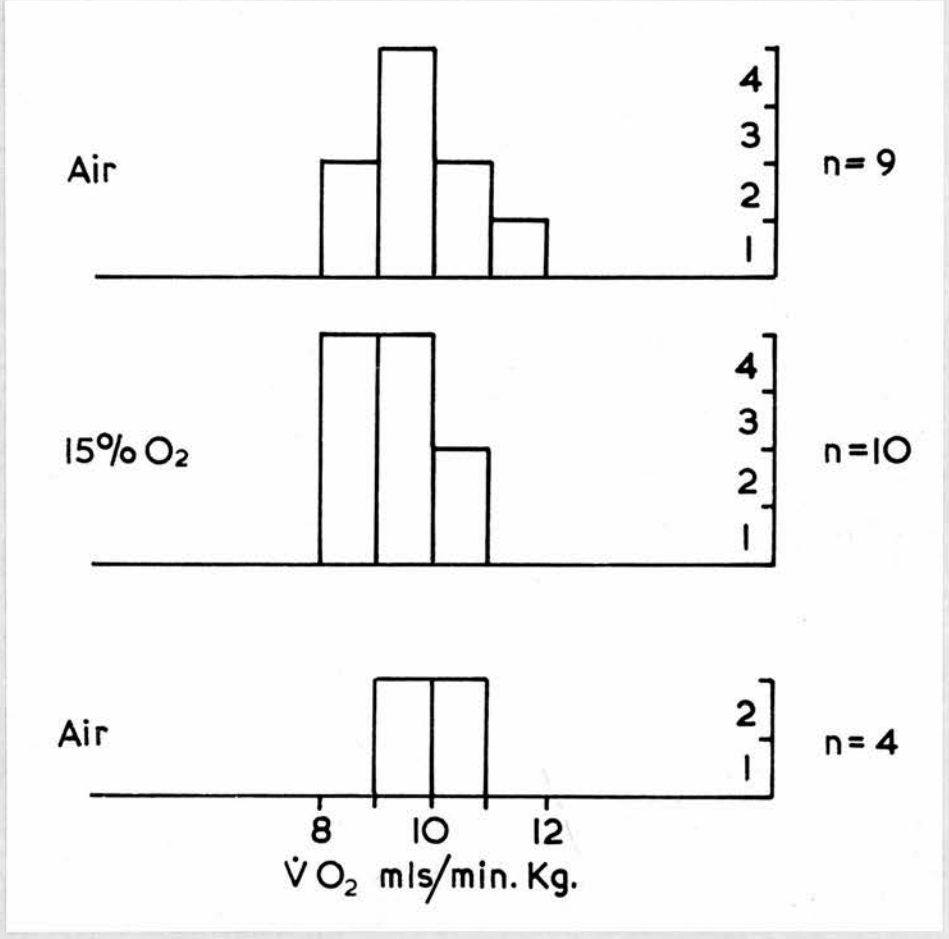


Fig. 37. Frequency distributions of measurements of oxygen consumption ($\dot{V}O_2$) in air (Period 1) followed by 15% oxygen (Period 2) and air (Period 3). Babies clothed with vest, nightdress and nappy but <u>without</u> a sheet in the cool.

TABLE 12A

OXYGEN CONSUMPTION OF FULLY CLOTHED BABIES IN THE COOL WHEN BREATHING AIR OR 15% OXYGEN

Exp. No.	Age	Wt (kg)	Sex	Basal O_2 cons. ml/min kg	Env. Temp.	Period I : Air					Period II : 15% O_2						Period III : Air					
						Activity	O_2 Cons. ml/min kg	% inc. Above B.M.R	1 SD	1 SE	Activity	O_2 Cons. ml/min kg	1 SD	1 SE	% Change II on I	% O_2	Activity	O_2 Cons. ml/min kg	1 SD	1 SE	% Change III on I	% Change III on II
88B	6 days	4.00	F	6.6	26	1.1	7.60	15	1.31	0.29	1.0	7.65	1.00	0.22	+ 1	14.8						
88C	6 days	4.05	F	6.6	25	1.0	7.53	14	0.58	0.13	1.2	8.49	1.06	0.24	+13	14.9	1.0	8.36	0.73	0.16	+11	- 2
89A	6 days	3.90	M	7.7	24						1.2	8.28	2.05	0.46		13.3	1.0	8.52	0.84	0.19		+ 3
91A	4 days	3.48	F	6.6	24	1.0	8.33	26	1.67	0.37	1.0	8.91	1.27	0.28	+ 7	14.9	1.1	8.81	1.58	0.35	+ 3	- 1
92A	1 day	3.45	F	6.6	24	1.0	9.81	49	1.12	0.25	1.4	10.50	3.17	0.71	+ 7	15.3						
93A	3 days	3.45	M	7.2	24						1.0	9.47	1.08	0.24		13.2	1.0	9.44	1.10	0.25		0
93B	4 days	3.51	M	6.4	24	1.1	8.63	35	1.70	0.38	1.1	9.44	1.00	0.22	+ 9	15.3	1.3	9.54	1.94	0.43	+11	+ 1
96A	20 hrs	3.02	M	6.8	27	1.2	8.62	27	1.24	0.28	1.1	8.04	1.68	0.38	- 7	15.7	1.0	8.93	1.16	0.26	+ 4	+11
97A	20 hrs	3.48	F	6.6	28	1.2	9.23	40	1.07	0.24	1.1	9.62	1.33	0.30	+ 4	14.6	1.3	9.17	1.40	0.31	- 1	- 5
98A	7 hrs	3.10	M	5.2	28	1.0	7.21	39	0.87	0.20	1.0	6.74	0.78	0.18	- 7	14.9						
98A	9 hrs	3.10	M	5.2	27	1.0	6.20	19	0.93	0.21	1.0	6.80	1.03	0.23	+10	15.2	1.0	6.14	1.34	0.30	- 1	-11
Mean	2.9 days (n=11)	3.50		6.50	26	1.1	8.13 (n=9)	30	1.10	0.37	1.1	8.54 (n=11)	1.19	0.36	+ 4	14.7	1.1	8.61 (n=8)	1.08	0.38	+ 4.5	-0.5

TABLE 12B

STATISTICAL TESTS OF SIGNIFICANCE ON TABLE 12A

Subject	Mean mls/min per Kg.	S.D.	Significance of difference between means	Statistical Data
Oxygen consumption in Period 1 AIR	8.13	1.10	0.5>P>0.4 (t = 0.79)	At 18 degrees of freedom P = 0.5 t = 0.69 P = 0.4 t = 0.86
Oxygen consumption in Period 2 15% O_2	8.54	1.19		
Oxygen consumption in Period 2 15% O_2	8.54	1.19	0.9>P>0.8 (t = 0.13)	At 17 degrees of freedom P = 0.9 t = 0.128 P = 0.8 t = 0.257
Oxygen consumption in Period 3 AIR	8.61	1.08		
Oxygen consumption in Period 1 AIR	8.13	1.10	0.4>P>0.3 (t = 0.91)	At 15 degrees of freedom P = 0.4 t = 0.87 P = 0.3 t = 1.07
Oxygen consumption in Period 3 AIR	8.61	1.08		

Subject	Mean %	S.D.	Significance of difference from zero	
% change of Period 2 on Period 1, i.e. oxygen consumption in Period 2 -oxygen consumption in Period 1 as a percentage of that in Period 1	+ 4	7.2	0.2>P>0.1 (t = 1.72)	At 8 degrees of freedom P = 0.2 t = 1.40 P = 0.1 t = 1.86
% change of Period 3 on Period 2	- 0.5	6.3	0.9>P>0.8 (t = 0.22)	At 7 degrees of freedom P = 0.9 t = 0.13 P = 0.8 t = 0.26
% change of Period 3 on Period 1	+ 4.5	5.4	0.2>P>0.1 (t = 2.05)	At 5 degrees of freedom P = 0.2 t = 1.48 P = 0.1 t = 2.02

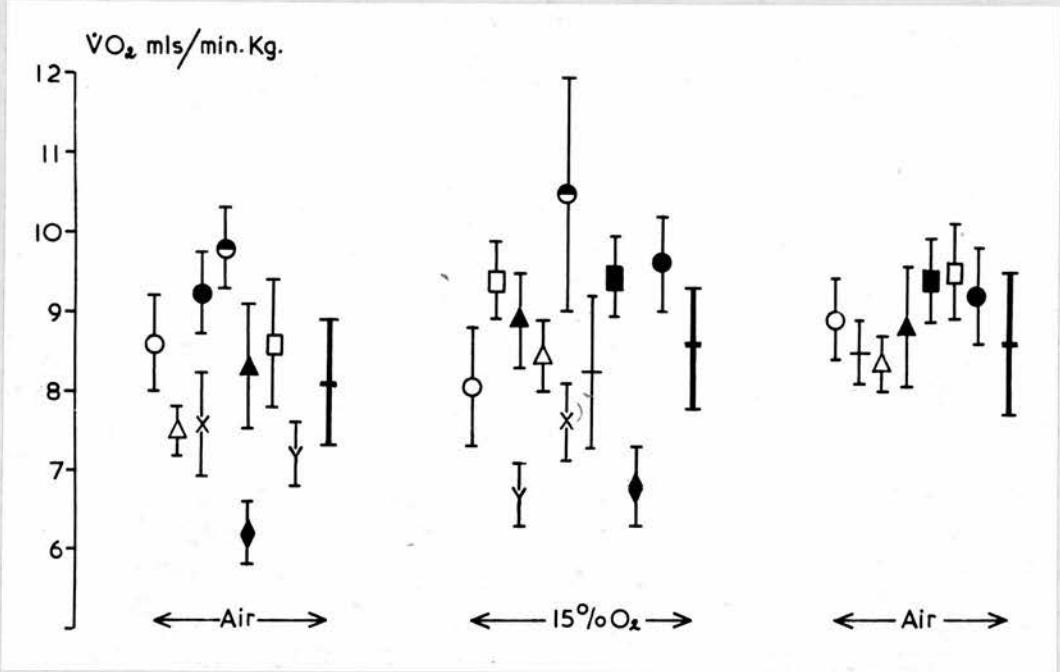


Fig. 38. Measurements of oxygen consumption ($\dot{V}O_2$) in mls/min. Kg. in babies clothed with vest, nightdress, nappy and sheet. In a cool environment breathing air, 15% oxygen and air. Results from the same baby at the same environmental temperature are shown by the same symbol which indicates the mean. ⊤ indicates 95% confidence limits of mean.

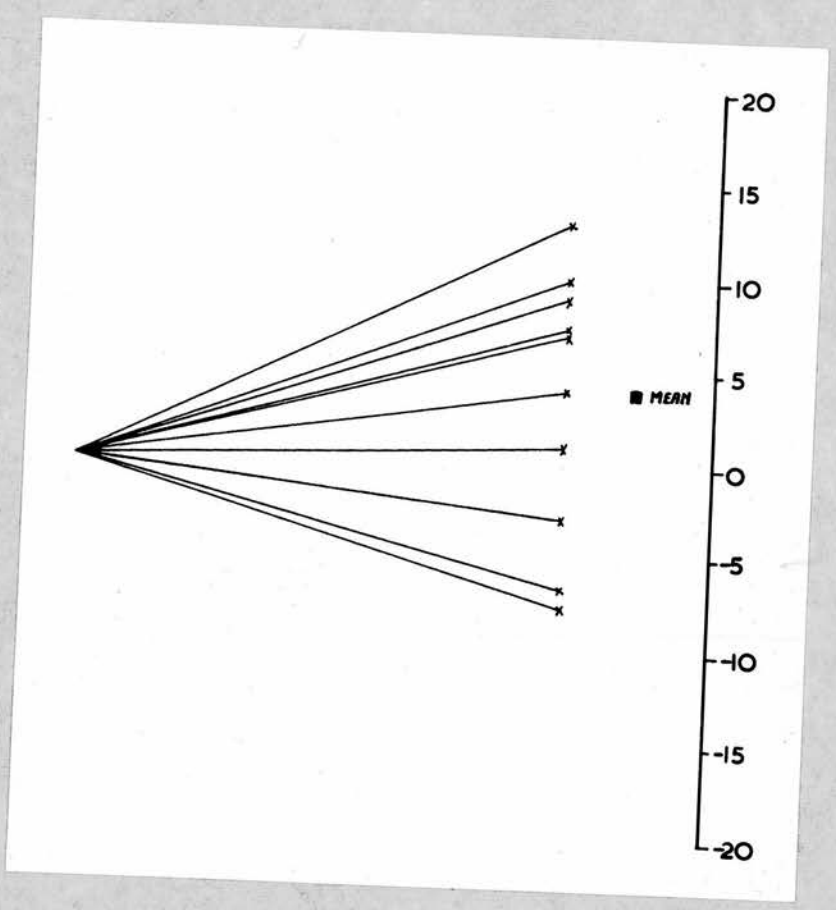


Fig. 39. Percentage changes in oxygen consumption on breathing 15% oxygen for fully clothed babies in a cool environment. Symbols as in Fig. 30.

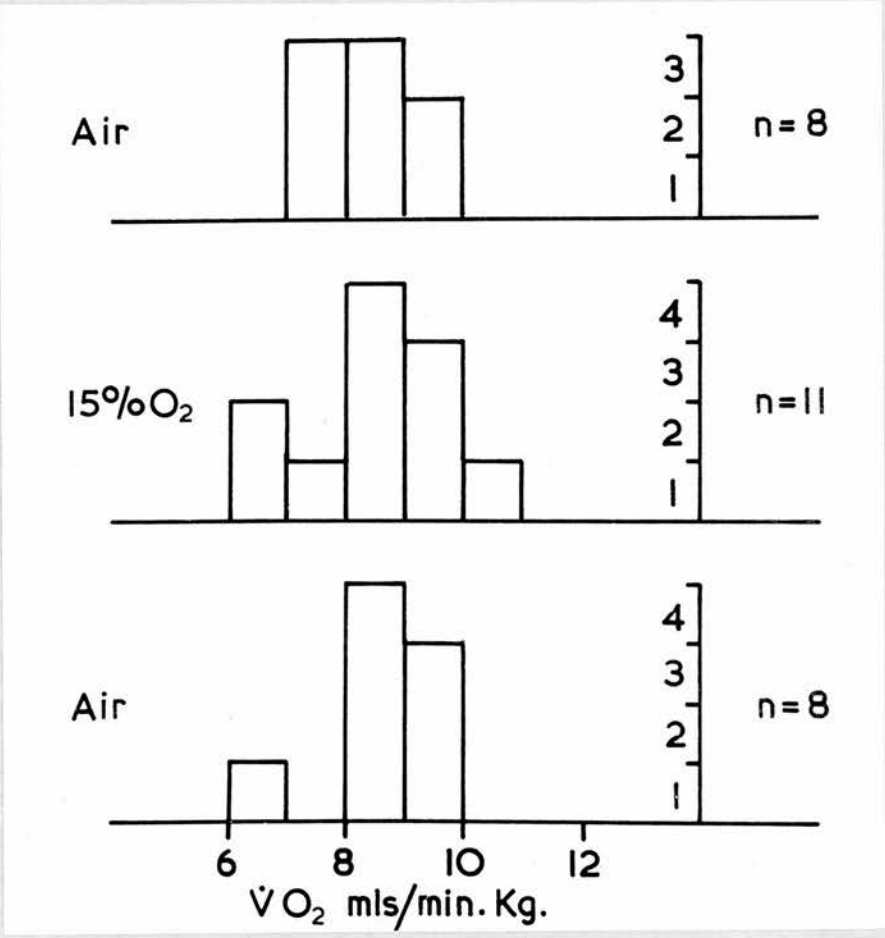


Fig. 40. Frequency distribution of measurements of $\dot{V}O_2$ in air (Period 1) followed by 15% oxygen (Period 2) and air (Period 3). Babies clothed with vest, nightdress, nappy and sheet.

Results (cont'd).

measurements exceed the range which contains 98% of all basal metabolic rates (according to Hill and Rahimtulla, 1965), but in Table 12 many of the results are within this range, although the smallest increase over the basal metabolic rate was 13.6%. This was done to imitate the results of Oliver and Karlberg as closely as possible, see later page 116.

In Tables 13a and 13b are shown the babies in whom the activity in air or 15% oxygen exceeded 1.5 arbitary units and in whom activity was considered to have a significant effect on oxygen consumption. The results from this Table show again that 15% oxygen had no significant effect on oxygen consumption. These results are included for completeness, and are not further considered even though Hill (1959) showed that oxygen consumption fell in spite of activity when kittens were breathing low oxygen mixtures.

Reproducibility in the Cool.

The change in oxygen consumption between period 1 and period 3 in Tables 10, 11 and 12 gives an estimate of the amount of variation to be expected under identical thermal conditions in air in the cool 20-60 minutes apart (Table 14). The values for the mean and standard deviation of the change in oxygen consumption expressed as a percentage are almost exactly the same as those found in the warm. However if the babies who were active in the cool had been included the range of variation would have been much greater.

A calculation similar to that in Appendix 2 shows that the method, and this range of variation, would easily be sensitive enough to detect a mean fall in oxygen consumption in 15% oxygen of 17% (provided the amount of

TABLE 13A

ACTIVE BABIES (NAKED)

					Period I : Air				Period II : 15% O_2					Period III : Air					
Exp. No.	Age in Days	Wt. kg.	Sex	Env. Temp.	Activity	O_2 cons. ml/min. per kg.	1 SD	1 SE	Activity	O_2 cons. ml/min. per kg.	1 SD	1 SE	% change of II on I	% O_2	Activity	O_2 cons. ml/min per kg.	1 SD	1 SE	% change III on I	% change III on II
4B	4	3.68	M	30	1.8	9.41	1.95	0.49	2.8	9.93	1.57	0.39	+ 6	14.0	2.0	10.58	3.57	0.89	+12	+ 6
5B	2	2.76	M	30	2.5	9.80	3.43	0.86	1.3	7.70	0.91	0.23	-11	15.0	3.8	12.80	4.28	1.07	+31	+66
5E	9	3.02	M	28	1.0	9.40	0.41	0.10	2.3	10.90	2.62	0.95	+16	14.0	1.5	11.20	2.58	0.65	+19	+ 3
6C	2.5	3.05	F	28	1.8	9.77	1.98	0.44	1.2	9.28	2.15	0.48	- 5	15.0	1.4	10.00	3.28	0.73	+ 2	+ 8
66D	4	3.36	M	24	1.9	14.43	2.86	0.65	3.0	14.18	2.70	0.60	- 2	14.5	2.6	17.52	3.40	0.76	+21	+24
66E	7	3.60	M	24	2.9	13.44	3.63	0.81	3.8	16.99	2.23	0.50	+26	14.5	3.0	16.38	2.74	0.61	+22	- 4
69A	0.25	4.25	M	26	2.0	8.64	3.48	0.79	3.0	9.87	2.80	0.70	+14	15.0	-	-				
69B	2.2	4.03	M	24	3.0	14.63	3.25	0.73	1.3	10.16	2.11	0.47	-30	15.0	1.6	13.77	4.47	1.00	- 6	+36
69C	4	4.17	M	26	1.3	8.68	2.52	0.56	2.4	13.72	4.67	1.05	-58	15.0	1.5	9.22	2.14	0.48	+ 6	-33
69E	7	4.25	M	24	3.6	19.18	1.97	0.44	3.5	14.68	5.47	1.22	-23	14.5	3.6	16.45	8.27	1.08	-14	+12
73A	4	3.35	F	29	1.7	8.05	1.80	0.40	1.4	7.52	0.85	0.19	- 7	15.0	2.9	10.46	2.57	0.58	+30	+39
73A	4	3.35	F	31	1.4	7.96	1.62	0.36	2.4	8.93	2.82	0.63	+12	14.5	-	-				
73B	5	3.35	F	30	1.3	7.47	2.76	0.62	3.0	7.93	1.52	0.34	+ 6	15.0	-	-				
79C**	8	2.87	F	24	1.2	11.86	3.74	0.84	2.5	13.56	4.75	1.06	+14	15.2	-	-				
82B*	3	3.35	F	22	2.0	10.32	1.38	0.31	2.8	13.88	4.33	0.97	+35	13.5	-	-				
82C*	5	3.45	F	23	1.5	10.28	1.65	0.37	2.2	13.23	2.74	0.61	+29	14.0	1.9	12.46	2.32	0.52	+12	- 6
84A*	6	3.45	F	31	1.2	7.93	2.16	0.48	2.7	10.54	4.52	1.01	+33	15.5	-	-				
91B*	5	3.55	F	24	2.3	10.13	4.19	0.94	2.2	9.95	2.16	0.48	- 2	15.0	-	-				
93B*	4	3.51	M	24	1.6	9.95	1.71	0.38	1.4	12.26	2.12	0.47	+23	15.5	-	-				
MEAN	4.5	3.49		26.4	1.80	10.60 (n = 19)	2.95	0.70	2.37	11.33 (n = 19)	2.69	0.63	+10.1	14.72	2.34	12.80 (n=11)	2.88	0.87	+12 (n=11)	+14 (n=11)

* Clothed as in Table 12

** Clothed as in Table 11

TABLE 13B

STATISTICAL TESTS OF SIGNIFICANCE ON TABLE 13A

Subject	Mean mls/min per Kg.	S.D.	Significance of difference between means	Statistical Data
Period 1 AIR	10.60	2.95)		
		)	0.50>P>0.40	At 36 degrees of freedom
Period 2 (15% O_2)	11.33	2.69)	(t = 0.80)	P = 0.50 t = 0.68 P = 0.40 t = 0.85
Period 2 (15% O_2)	11.33	2.69)		
		)	0.20>P>0.10	At 28 degrees of freedom
Period 3 AIR	12.80	2.88)	(t = 1.39)	P = 0.20 t = 1.31 P = 0.10 t = 1.70
Period 1 AIR	10.60	2.95)		
		)	0.10>P>0.05	At 28 degrees of freedom
Period 3 AIR	12.80	2.88)	(t = 1.98)	P = 0.10 t = 1.70 P = 0.05 t = 2.05

Subject	Mean (%)	S.D.	Significance of difference from zero	Statistical Data
% change of Period 2 on Period 1	+ 10.1	21.5	0.10>P>0.05 (t = 2.05)	At 18 degrees of freedom P = 0.10 t = 1.73 P = 0.05 t = 2.10
% change of Period 3 on Period 2	+ 14	26.6	0.20>P>0.10 (t = 1.74)	At 10 degrees of freedom P = 0.10 t = 1.81 P = 0.20 t = 1.37
% change of Period 3 on Period 1	+ 12	14.5	0.05>P>0.02 (t = 2.75)	At 10 degrees of freedom P = 0.05 t = 2.23 P = 0.02 t = 2.76

TABLE 14

REPRODUCIBILITY IN THE COOL IN QUIET BABIES

	n	Mean %	1 SD%	1 SEM%	Significance of difference from zero
Change in oxygen consumption (Period 3 - Period 1) as a % of that in Period 1 (from Tables 10, 11,12)	13	0.7	9.5	2.6	$0.8>P>0.7$ ($t = 0.26$)

Results (cont'd).

variation in oxygen consumption from air to 15% oxygen remains the same as that in air to air). If the mean of five observations of oxygen consumption in 15% oxygen was 17% less than that in air, the results would be statistically significant at the 1% level, and similarly 8 for the 0.1% level.

Results (cont'd).

Effect of Other Variables

Environmental Temperature.

Hensel (1953) found that cold receptors in the cat tongue exhibit a steady discharge frequency which depends on absolute temperature and is inhibited by hypoxia. In view of this finding the results were examined for evidence of any variation in the effect of hypoxia at different environmental temperatures. Fig. 41 shows that the oxygen consumption increases in lower environmental temperatures and as expected the increase is smaller in the clothed infants. The increases and decreases in metabolism, if any, during 15% oxygen are equally distributed at different environmental temperatures and no one temperature can be selected as being more conducive to a fall in 15% oxygen than any other.

The Amount of Metabolic Response to Cold and the Effect of Hypoxia.

In the work of Hill (1959) with kittens low oxygen mixtures had a more striking effect if the metabolism had been increased by exposing the kittens to low environmental temperatures. Dawes, Jacobson, Mott and Shelley (1960) showed that in infant Rhesus monkeys low oxygen depressed the increase in metabolism provoked by exposure to environmental temperatures of 22-24^{o}C but the same amount of hypoxia did not affect oxygen consumption in the warm. Adamsons (1959) made a similar observation in the newborn rat. Hemingway and Birzis (1958) found that 13-8% oxygen did not affect the oxygen consumption of non shivering decerebrate cats but that the same amount of hypoxia lowered metabolism of shivering intact cats to basal levels.

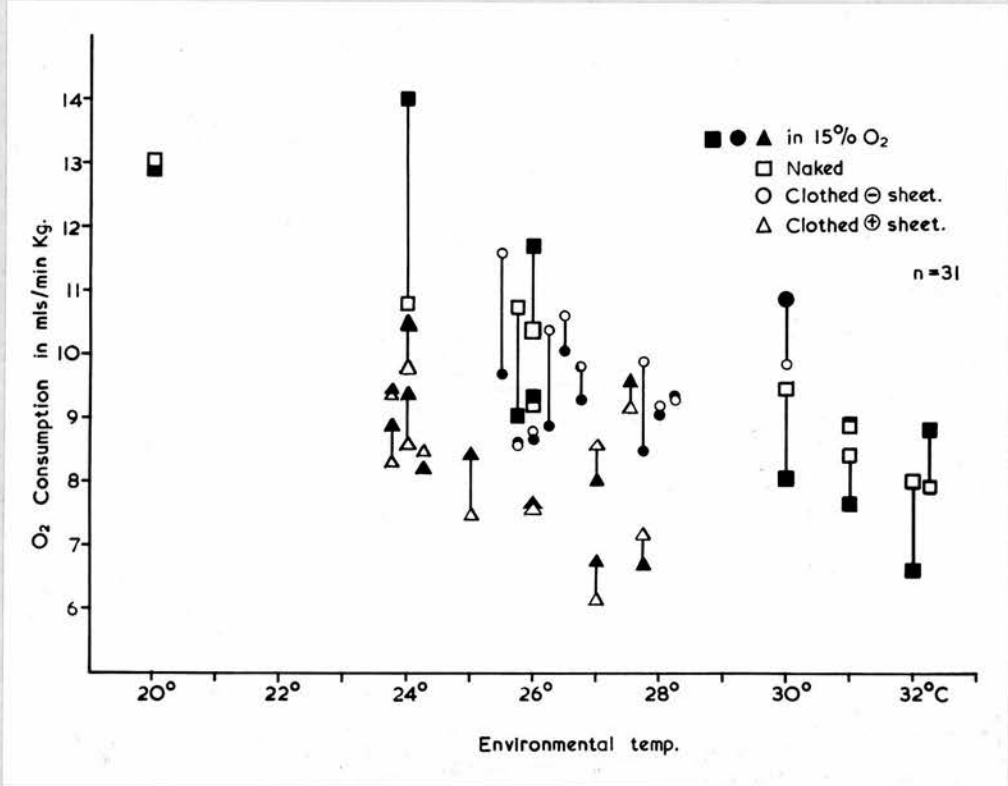


Fig. 41. Change in oxygen consumption when breathing 15% oxygen, related to environmental temperature in naked babies, and babies clothed with and without a sheet.

Results (cont'd).

In the present work the presence and absence of clothing meant that the increase in metabolism was not always directly related to environmental temperature. Nor was the measured environmental temperature directly comparable to that in the work of Oliver and Karlberg (1963). The cold stimulus of the babies was not easily assessed and it was felt that it would be better to judge it by measuring the increase in oxygen consumption that it provoked. As mentioned previously the basal metabolic rate was measured before the infant was exposed to the cold, and the metabolic response to the cold could be expressed as the percentage increase in oxygen consumption above the basal rate. This is shown in Tables 10, 11 and 12 and the mean increase is 44%. The increase in metabolism can be compared with that found by the earlier workers. In the experiments of Cross et al. in 1958 the mean oxygen consumption in air before 15% oxygen was 7.73 mls/min./Kg. The individual measurements for babies of different ages show a mean increase above the B.M.R. for their age, as determined by Hill and Rahimtulla (1965) of about 25%. This increase indicates that the babies were not in a basal state.

The estimate of Oliver and Karlberg (1963) for B.M.R. agrees closely with the standards of Benedict and Talbot (1915), Brück (1961) and Hill and Rahimtulla (1965). Their mean value for oxygen consumption in cool air before 15% oxygen (see Table 1) is about 30% greater than their estimate for the basal metabolic rate. In our work Table 12 shows the results on clothed babies, with a mean increase in metabolic rate directly comparable with that of Oliver and Karlberg (1963). The effects of 15% oxygen in the experiments reported here have been plotted against

Results (cont'd).

the percentage increase above B.M.R. in Fig. 42 and although the increase in metabolism extends from 14% to 111% there is no evidence of a fall in oxygen consumption at any point.

Concentration of Oxygen Used.

The different low oxygen mixtures added to the circuit produced slightly different concentrations of oxygen, although the mean oxygen concentration was 15%. When the oxygen concentration had been lowered it remained constant. The actual concentrations achieved are shown in the Tables, and varied from 13.3 to 16.1% oxygen. Many of the workers with hypoxia in animals, (see Discussion page 122), have shown that oxygen concentrations below 15% have marked effect on oxygen consumption. In Fig. 43 the change in oxygen consumption is plotted against the oxygen concentration used. There is no evidence of a threshold value below which oxygen consumption consistently fell.

The concentration of oxygen breathed before and after 15% oxygen was not always exactly the same as that of oxygen in air. This was because 100% oxygen was added to the circuit to change the oxygen concentration more rapidly. This raises the possibility that the change in oxygen concentration from "air" to "15%" oxygen may be related to the change in oxygen consumption; Fig. 44 shows that the amount of change in oxygen concentration is not related to the change in metabolism.

Duration of Hypoxia.

Cross et al. (1958) found that oxygen consumption fell 5.8% in the second period of exposure to 15% oxygen, which suggests that the longer the infant is exposed to 15% oxygen the greater would be the depression of oxygen consumption. On the other hand Fluckiger (1956) showed

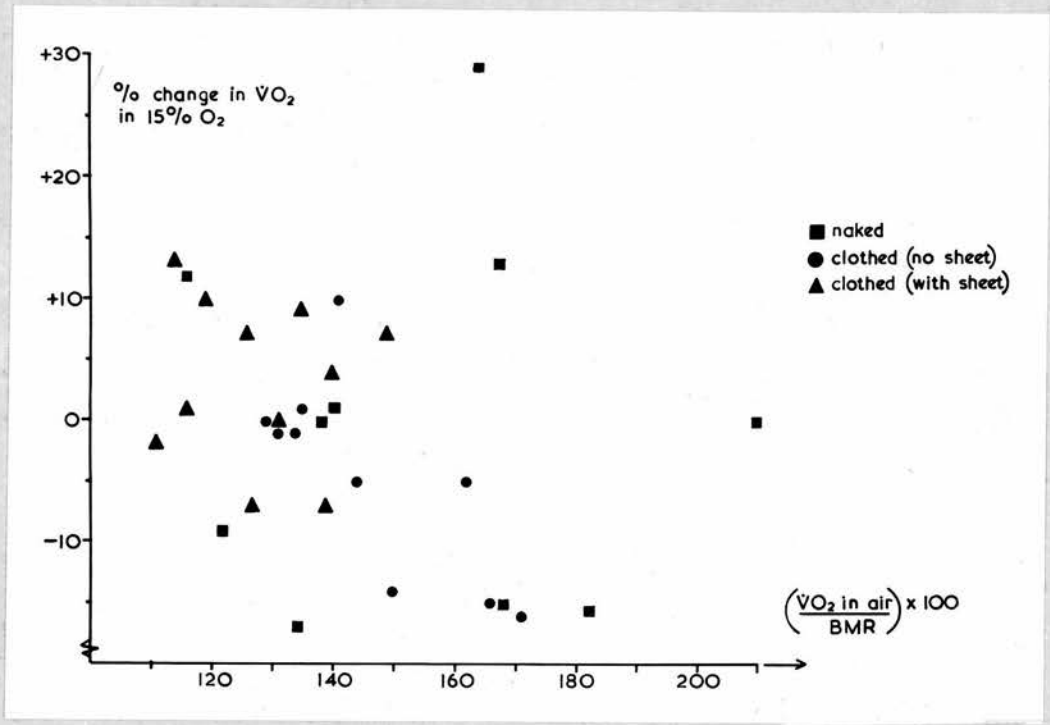


Fig. 42. Percentage change in oxygen consumption ($\dot{V}O_2$) in 15% oxygen plotted against the metabolic rate in Period 1 (air) expressed as a percentage of the basal metabolic rate. (From Tables 10, 11 and 12. n = 31).

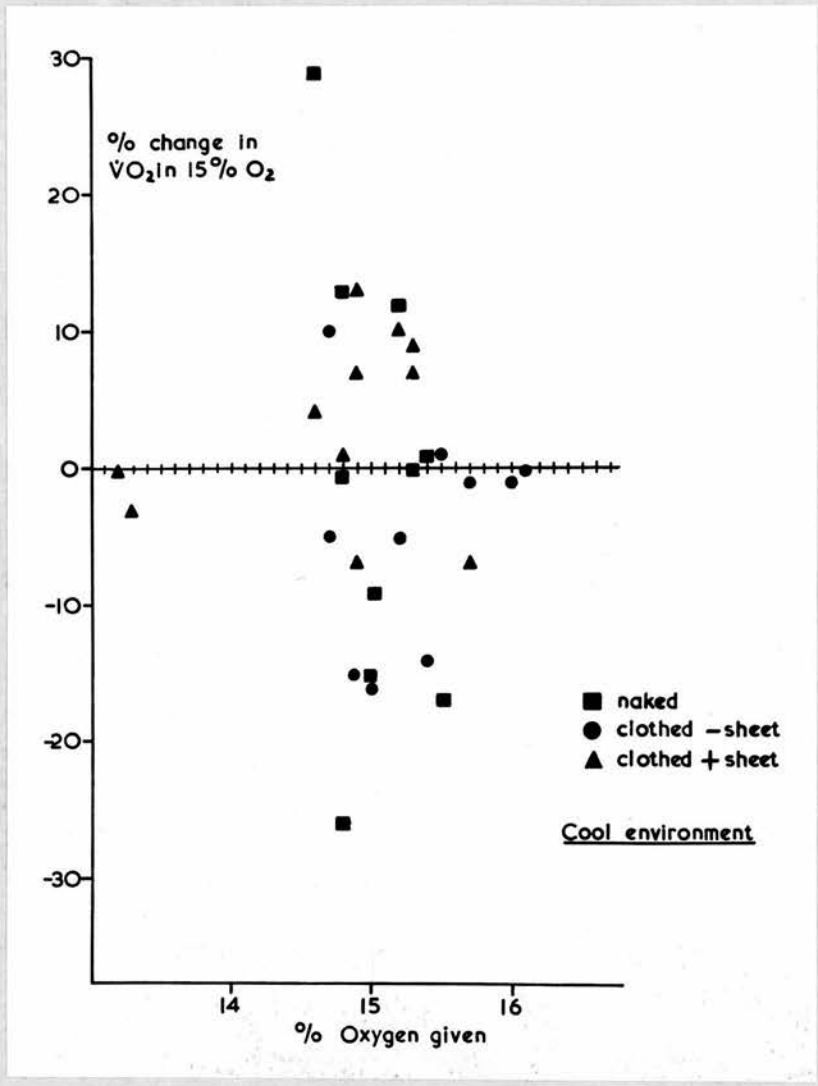


Fig. 43. Percentage change in oxygen consumption during hypoxia, plotted against concentration of oxygen given in "15%" oxygen.

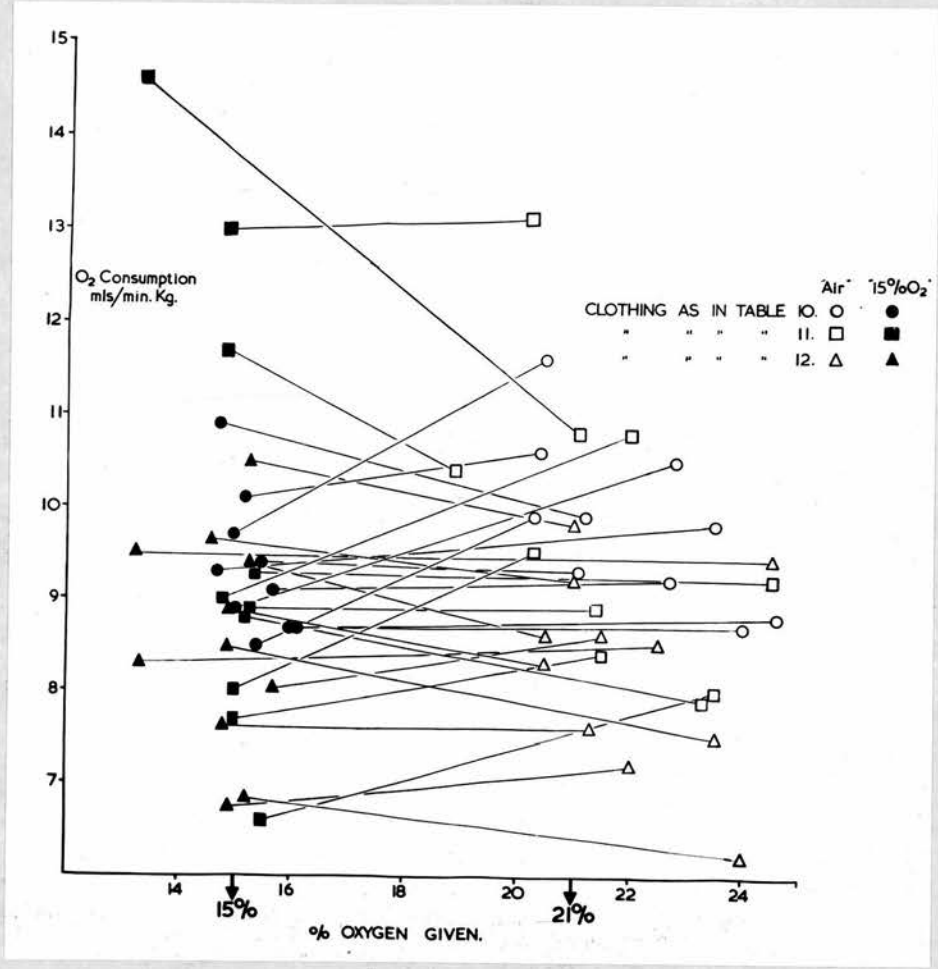


Fig. 44. Change in oxygen consumption and change in oxygen concentration from "air" to "15% oxygen". Members of a pair of observations are joined by lines.

Results (cont'd).

that if rats were kept in the equivalent of 10% oxygen for several days the rectal temperature gradually rose to normal levels over 3-4 days, and that the oxygen consumption approached values in air over a definitely longer time interval. Similarly Blatteis (1964) working with newborn rabbits found that after an exposure of several hours to low concentrations of oxygen the oxygen consumption began to rise after the initial fall. (See also Hemingway and Nahas, 1952). In our work babies were exposed to 15% oxygen for as long as 45 mins. but the oxygen consumption did not change (see Fig. 45). This is in accord with the findings of Hill (1959) in a kitten exposed to 10% oxygen for 1½ hours. (See her Fig. 5).

Age and Change in Oxygen Consumption.

Taylor (1960) found that the oxygen consumption in rats, aged less than 24 hours, in the warm, was inhibited by 18% oxygen although in rats of a few days old 15% oxygen had no effect on oxygen consumption in the warm. On the other hand Cross, Dawes and Mott (1959) found that in newborn lambs in the warm a given amount of hypoxia lowered oxygen consumption more at the age of 1-10 days than at ages less than 1 day.

Graham (1959) found that the oxygen tension of normal newborn infants of 3 to 50 hours was consistently lower than in the adult (mean 74 mls. Hg.). During this period hypoxia might lower the arterial pO_2 more than when the baby was older, and breathing 15% oxygen at this age might affect oxygen consumption more than later. The results have been analysed for the effect of age for babies in the warm in Fig. 46, and in Fig. 47 for babies in the cool, but there is no relationship to age.

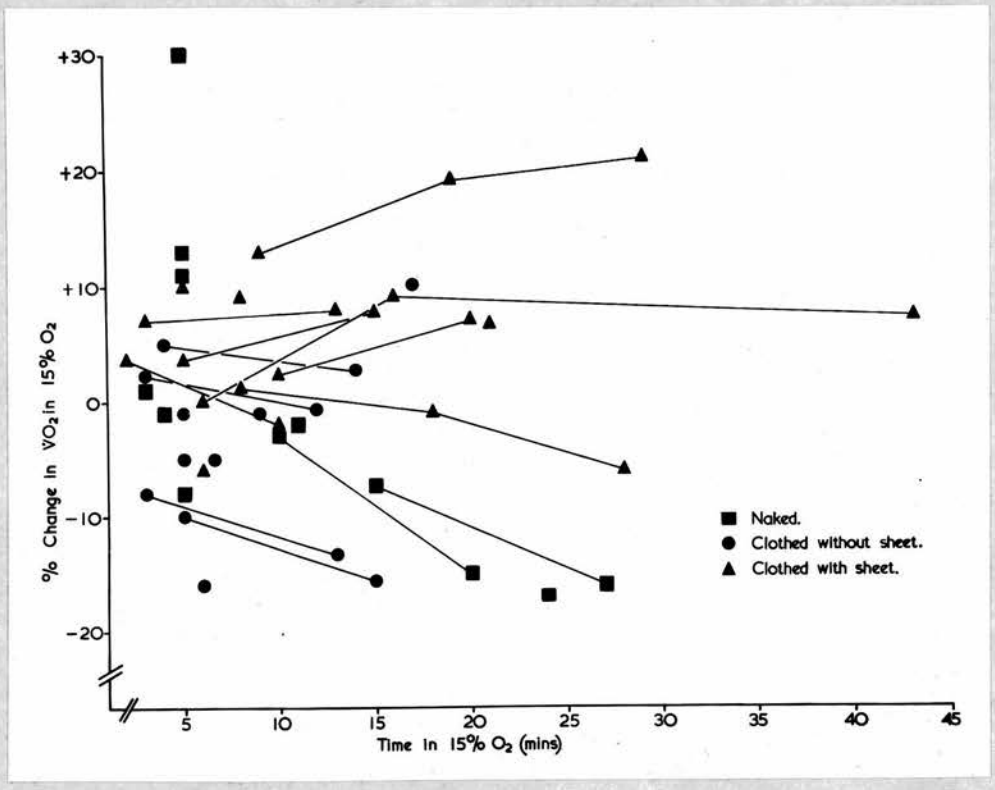


Fig. 45. Percentage change in oxygen consumption in 15% oxygen and time in 15% oxygen.

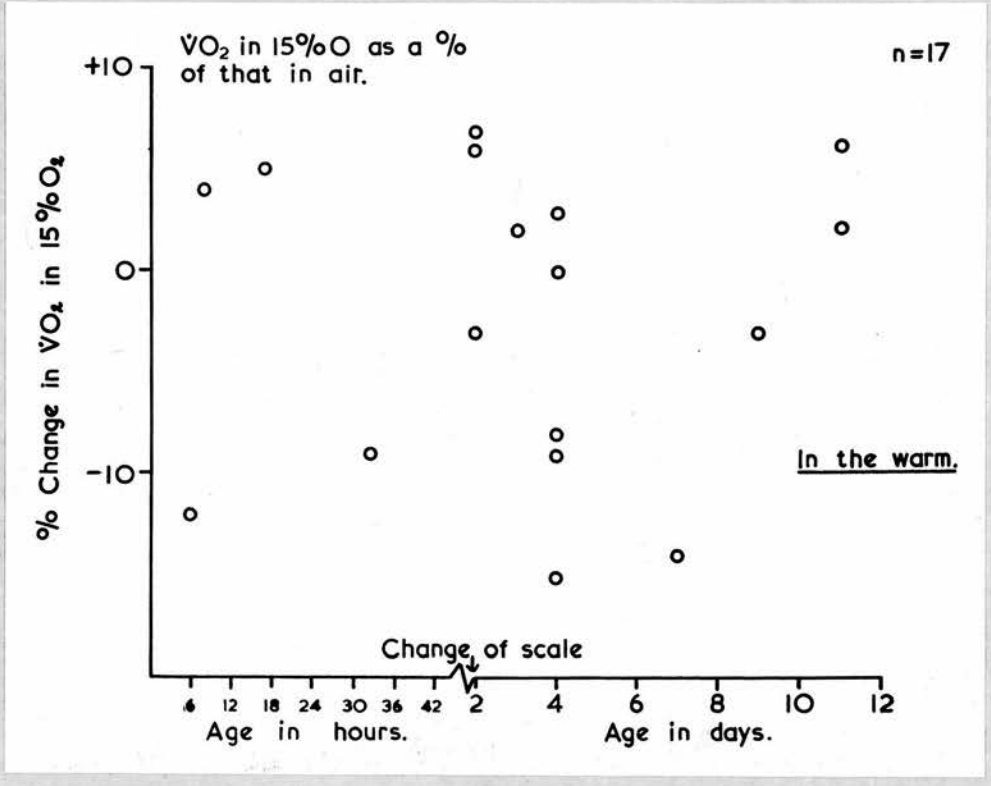


Fig. 46. Percentage changes in oxygen consumption in 15% oxygen, plotted against age. (n = 17). For babies in the WARM.

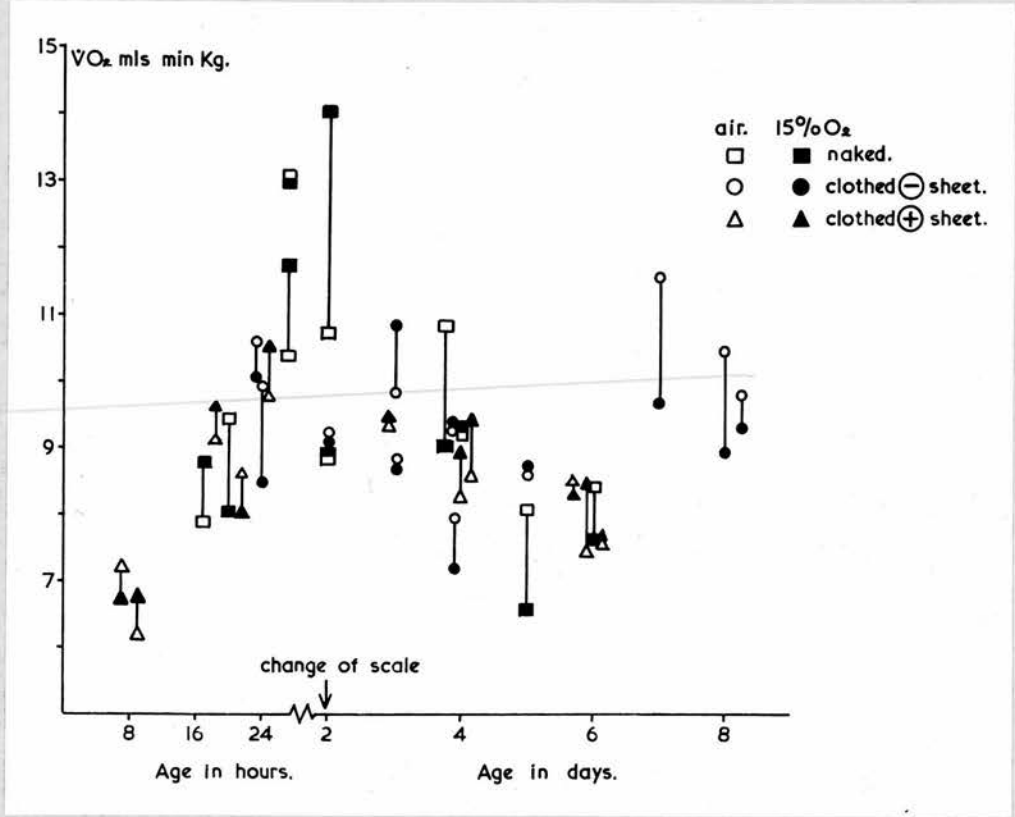


Fig. 47. Oxygen consumption in air (open symbols) and in 15% oxygen (closed symbols) expressed as mls/min. Kg. plotted against age in hours and days (interrupted scale). In the COOL.

Results (cont'd).

Rectal Temperature.

Except in the very early experiments or when the rectal thermo-couple was removed to try to quieten a very active baby, rectal temperature was measured continuously. The initial rectal temperature of all infants varied between 36.4 and 37.2°C. Table 15 shows the changes in rectal temperature during the measurements of oxygen consumption reported in Tables 9-12 inclusive. It will be seen that rectal temperature tends to rise in the warm and to fall in the cool even though the oxygen consumption was far below the maximum possible. (Infants a few hours old can double or treble their oxygen consumption in the cool (Brück, 1961; Hill and Rahimtulla, 1965; Adamsons et al. 1965)). Although diminished oxygen consumption and heat production in 15% oxygen would tend to lower rectal temperature provided thermal conductance remained constant, the fall in rectal temperature in infants in the cool breathing 15% oxygen is no different from that when they are breathing air.

Effect of Lowering the Environmental Temperature during Hypoxia.

After it was noted that the oxygen consumption in the cool was maintained during hypoxia at the same level as in the preceeding air, the environmental temperature was lowered while one baby was breathing 15% oxygen. The oxygen consumption was then compared with that in air following. There was no significant change in oxygen consumption in 15% oxygen.

TABLE 15

MEAN CHANGE IN RECTAL TEMPERATURE IN QUIET INFANTS BREATHING AIR OR 15% OXYGEN

(The results are calculated from the rectal temperatures recorded at the same time as the mean values for oxygen consumption in 10 min. periods in Tables 9-12 inclusive)

ENV. TEMP.	AIR mean change in rectal temp. °C	15% OXYGEN mean change in rectal temp. °C	AIR mean change in rectal temp. °C
WARM	Rise 0.06 n = 8	Rise 0.03 n = 8	Rise 0.05 n = 8
COOL			
1. Naked from Table 10	Fall 0.11 n = 8	Fall 0.04 n = 8	Fall 0.05 n = 2
2. Clothed from Table 11	--- 0.00 n = 9	Fall 0.06 n = 9	Rise 0.03 n = 3
3. Clothed from Table 12	Fall 0.10 n = 8	Fall 0.02 n = 9	Fall 0.05 n = 7

Results (cont'd).

INCIDENTAL OBSERVATIONS

Activity.

Cross et al. (1958) found that after 15% oxygen infants tended to appear sleepy and feel flaccid. To investigate this in the infants studied here the mean activities in every period of 15% oxygen and in every period in air at the same temperature (in the cool) are shown in Table 16; this includes all the measurements in cool air or 15% oxygen including those in which the baby had a high activity and which were excluded from Tables 10, 11 and 12. The results have not been analysed statistically but there seems to be little change in activity. It is essential to note that Hill (1959) found that oxygen consumption was still lowered even in kittens who were active while breathing low oxygen mixtures.

Cyanosis.

Cyanosis was looked for on all occasions before and during 15% oxygen, but was seen on the lips in only a few infants who were breathing 15% oxygen and crying at the same time. As peripheral cyanosis of the lips is seen in many infants while crying and breathing air this is not of significance. Cyanosis was never seen in a quiet infant breathing 15% oxygen. Sjöstedt and Rooth (1957) did not see cyanosis in infants exposed to 15% oxygen for therapeutic reasons for as long as one week.

Pallor and Shivering.

Pallor was noted in four infants exposed to 15% oxygen and when air was admitted a definite flush was seen. Skin vasoconstriction is a well known accompaniment of hypoxia, (Keele and Neil, 1963). The flushing after air was admitted may be the same phenomenon as the immediate feeling of warmth remarked on by aviators and mountaineers

TABLE 16

MEAN ACTIVITIES IN AIR, 15% OXYGEN, AND AIR

	Mean activity	n
AIR 1	1.68	n = 52
15% O_2	1.51	n = 77
AIR 2	1.67	n = 41

Results (cont'd).

breathing 100% oxygen after breathing air at high altitude. (Mentioned by Burton and Edholm, 1955, in a different context). Shivering was not seen.

Posture.

It was noted that in the warm babies tended to lie with the arms abducted, exposing the axillae. This was most noticeable in the smaller infants who had more room in the chamber. Exposure of the axillae would tend to increase heat loss. Mott (1963) described some of the behavioural responses which reduce heat loss in newborn animals.

CHAPTER 4
DISCUSSION

CONTENTS OF DISCUSSION

CONTENTS OF DISCUSSION (CONT'D).

DISCUSSION

CRITICAL CONCENTRATION OF OXYGEN IN INSPIRED GAS

This section examines the effect of concentrations of oxygen of about 15% on the oxygen consumption of newborn and adult animals. For this purpose work in which the oxygen concentration has been progressively lowered from 21% is of the most interest and these papers will be examined in most detail.

1. Newborn Animals.

After the work of Cross et al. (1958) many investigators examined the effect of hypoxia on newborn animals and although they came to the same general conclusion, many found that oxygen consumption in the cool in 15% oxygen was maintained at the same level as in air and that 15% oxygen did not depress metabolic response to cold.

Hill (1959) measured the oxygen consumption of kittens aged 0-40 days at environmental temperatures ranging from 22-36°C, and of adult guinea pigs at environmental temperatures ranging from 10-32°C, while the animals were breathing various concentrations of oxygen ranging from 24-6%. Her Figs. 7 and 9 show that only when they breathed less than 12% oxygen was there an unmistakable decrease in oxygen consumption.

Moore (1959) studied the oxygen consumption of kittens at an environmental temperature of 30°C, presumably below the neutral temperature zone, and found that the depression of aerobic metabolism was related to the degree of hypoxia. The threshold above which oxygen consumption was not lowered was 14%. His Fig. 6 shows that only when oxygen concentration was lowered to about 12% was there a clear fall in oxygen consumption.

Discussion (cont'd).

Moore (1956) used oxygen concentrations of 12.3 to 7.6% in his observations on newborn dogs in the cool and he found the oxygen consumption was diminished below control values in air.

Adamsons (1959) measured the oxygen consumption in young rabbits aged 0.5 to 60 days while they were breathing different concentrations of oxygen. In the cool as the oxygen content of the inspired gas was progressively reduced oxygen consumption decreased only when the concentration of oxygen breathed fell below 12%. Dawes, Jacobson, Mott and Shelley (1960) measured the oxygen consumption of six Rhesus monkeys in a cool environment and observed the effect of reducing the oxygen content of the inspired gas. They found that in the cool the percentage of oxygen breathed usually had to be reduced to less than 15% before there was significant fall in oxygen consumption. They stated, "There is in any event a quantitative difference between newborn monkeys and human babies because in the former the oxygen content of the inspired air had to be reduced below 13% before there was any consistent fall in oxygen consumption."

Fitzgerald (1953) studied the effect of progressively lowering the oxygen tension of inspired gas on the oxygen consumption of newborn mice. The oxygen consumption was unaffected until the oxygen tension of the atmosphere was 65 to 80 mm. Hg. which corresponds to 9 to 10.5% oxygen. The environmental temperature was not given in the original paper but Cassin (1963) stated that it was 35°C, so that these animals may have been in a warm environment.

Cassin (1963) studied the critical oxygen tension in newborn mice at different environmental temperatures.

Discussion (cont'd).

The oxygen tension in the inspired gas was progressively lowered and the point at which the oxygen consumption began to decrease was noted. The critical oxygen tension (pO_2) at 35°C environmental temperature was 85 mm. Hg. (10.2% O_2), at 30°C 115 mm. Hg. (15.2% O_2) and at 25°C 95 mm. Hg. (12.5% O_2). The mean oxygen consumption at the lower oxygen tension was only 4% less than at the higher pO_2. In all three examples the standard error of the mean oxygen consumption at the critical pO_2 overlapped the standard error of the mean at the next highest pO_2. At 30°C for example the standard error of the mean values for oxygen consumption overlapped that at higher oxygen tensions until the pO_2 was lowered to approximately 100 mm. Hg. (13.2% O_2) where the difference in the mean values for oxygen consumption was 17%. This is clear from Fig. 3 in Cassin's paper. In 5 day old mice the critical oxygen tension over a range of warm and cool temperatures was about 110 mm. Hg. (14.8% O_2).

The findings of Taylor (1960) appear to be exceptions to the general tendency that 15% oxygen does not affect oxygen consumption. In newborn rats less than 1 day old, in the neutral temperature zone, oxygen consumption fell when the animal was placed in 18% and 15% oxygen. This was quite unexpected. At the age of 3 to 4 days the oxygen consumption was well maintained despite 18% and 15% oxygen. However, Hill (unpublished observations) was unable to confirm this and on the contrary found, again in newborn rats, that in neutral environmental conditions, reducing the oxygen concentration to as low as 10% had no effect on oxygen consumption.

Discussion (cont'd).

The authors who used only a single oxygen concentration to induce hypoxia have employed much lesser concentrations than 15%. None have found that 15% oxygen lowers oxygen consumption. Cross et al. (1959) found that 10% oxygen suppressed shivering and diminished oxygen consumption in a 60 day old lamb. Blatteis (1964) used 10% oxygen in newborn rabbits and found that oxygen consumption fell about 50% in rabbits at an environmental temperature of about 25°C.

Moureck (1959) used 10% oxygen on young rabbits and demonstrated a 70% decrease in oxygen consumption at birth progressively decreasing to none at 4 weeks. The environmental temperature was between 32°C to 33°C.

2. Adult Animals.

Chevillard and Mayer (1935) reported that in adult mice at 21°C environmental temperature oxygen consumption fell by about 6% when the oxygen concentration breathed was reduced to 14.7% and the fall increased when the oxygen concentration was lowered to 13.6%. In the same subject Cassin (1963) showed that the critical oxygen tension at 28°C and less was 70 mm. Hg. (9.5% O_2), a lower figure than that reported by Chevillard and Mayer (1935).

Blood et al. (1949) measured the oxygen consumption of adult rats in a cool environment (18-20°C) in response to a progressive reduction in atmospheric pressure. Oxygen consumption did not fall until a simulated altitude of 15,000 ft. (approximately 11.8% oxygen) was reached. However, Giaja and Markovic (1948) found that the critical oxygen tension at an environmental temperature of 13-18°C for the adult warm adapted rat was 131 mm. Hg. (about 17% O_2) and for the cold adapted rat 106 mm. Hg. (about 13.5% O_2).

Discussion (cont'd).

Hemingway and Nahas (1952) studied the metabolism of adult dogs breathing air, 16% oxygen, 12% oxygen and 8% oxygen in the warm (24°C) and cool (12°C) environments. In 16% oxygen at an environmental temperature of 12°C the oxygen consumption did not fall below values in one of the control periods in air. Although there was no significant fall in oxygen consumption with 16% oxygen, 12% oxygen did produce a fall in metabolism.

Hemingway and Birzis (1956) using shivering lightly anaethetised cats progressively lowered the oxygen concentration to observe the effect on oxygen consumption; only when the oxygen concentration was between 13% and 8% did oxygen consumption diminish.

Pichotka and Scholtz (1959) found no evidence for a progressive fall in oxygen consumption or rectal temperature in adult guinea pigs at cool environmental temperatures when the concentration of the oxygen in the gas breathed was 15% and 12%. Only when the concentration of oxygen was reduced to 10% and 8% did the oxygen consumption show a progressive fall.

The work of Doi (1921), Ogata (1923), Harrison and Blalock (1927), Lewis and Gorlin (1952) and Gorlin and Lewis (1954), was mentioned in the introduction. None of these authors found that 15% oxygen lowered oxygen consumption.

Cordier and Mayer (1935) working with adult dogs found that the oxygen consumption did not fall until the oxygen concentration had been lowered to about 5%. Although the environmental temperature was not stated the fact that oxygen consumption was 7 mls/min/Kg. suggests that the animals were in the warm. Hamon et al.

Discussion (cont'd).

(1935) used 7% oxygen or less in experiments with adult rabbits, and made similar findings.

Conclusion. The author has been unable to find any work which disproves the conclusion that it appears that newborn infants are the only mammals, except for one report on the warm adapted rat, in which 15% oxygen has been shown to produce a substantial fall (17%) in the cool. Large falls in oxygen consumption have only been reported with oxygen concentrations significantly less than 15%.

Discussion (cont'd).

EFFECTS OF 15% OXYGEN IN BABIES.

The Present Work compared with Earlier Papers.

The work presented here is the first in which a normal oxygen consumption in babies in the cool breathing 15% oxygen has been reported and this result was completely unexpected. Our first impression was that it appeared to conflict completely with well established work on adult and newborn animals but a closer examination has shown that in fact the newborn infant is almost the only mammal in which 15% oxygen has been shown to lower oxygen consumption.

The present work will now be discussed in the light of the two earlier papers, (Cross et al. (1958); Oliver and Karlberg (1963).

Technical Differences.

The most obvious difference in technique between this and the earlier work on 15% oxygen in babies is that here a closed circuit apparatus was used and earlier workers (referred to above) used an open circuit. This in itself would not seem to be significant. The closed circuit apparatus gives values for oxygen consumption with a better time resolution than do open circuits. The values for basal metabolic rates agree closely with those found by Brück (1961) and Adamsons et al. (1965). Much of the earlier work on hypoxia in newborn animals and all the recent work was done using the closed circuit type of apparatus; the apparatus used for the experiments presented here was developed from one in which Hill (1959) successfully showed that low oxygen mixtures lowered the oxygen consumption in animals. Technical errors such as leaks out of or into the closed circuit were carefully excluded by weighted and unweighted leak tests performed

Discussion (cont'd).

before every experiment. Possible errors due to changes in temperature and humidity of the circuit gas were carefully avoided.

Procedural Differences.

As our result was unexpected repeated attempts were made while the work was in progress to reproduce the original conditions used by Cross et al. (1958) and Oliver and Karlberg (1963). The precautions taken to establish that the metabolic rate in air and 15% oxygen were compared in the cool, the effect of prolonged hypoxia, and the use of oxygen in concentrations slightly less than 15% have been described. The babies were studied not only while naked but also while clothed in the same manner as in the earlier work and the environmental temperature was adjusted to give the same increase above the basal metabolic rate.

The activity in the results reported was minimal and corresponds to that accepted by Oliver and Karlberg (1963). The degree of activity accepted has been shown not to exert a significant effect on oxygen consumption. Careful scrutiny of the work on hypoxia in newborn animals does not reveal any factor that was considered important and has been omitted from this study, except of course, for the effect of giving gases with an oxygen concentration less than 15%. The number of results presented is quite large enough to enable one to draw a satisfactory conclusion and in fact more observations are presented than in the two earlier papers combined.

Since the failure to confirm the previous results did not appear to be due to significant differences in experimental technique or procedure the original work was re-examined.

Discussion (cont'd).

Alveolar Oxygen and Carbon Dioxide Tensions in Cross et al. (1958).

From the original data (Cross et al., 1958) it was possible to calculate the mean alveolar tensions of oxygen and carbon dioxide. In Table 17 these are compared with values found by other investigators. These calculations taken at their face value suggest that in babies breathing air there was a certain degree of hypoxia and hypercapnia. It is less easy to comment on the values in the subjects breathing 15% oxygen because there are few other values of alveolar tensions of carbon dioxide and oxygen for comparison. However Graham (1959) found values for arterial oxygen tension (pO_2) of 47 mm. Hg. and 50 mm. Hg. in two babies breathing 15% oxygen. The difference between alveolar and arterial oxygen tensions is about 28 mm. Hg. in babies breathing air(Nelson, Prod'hom, Cherry, Lipsitz and Smith, 1963), so that the expected alveolar oxygen tension in babies breathing 15% oxygen is about 47 + 28 = 75 mm. Hg. We have calculated that the alveolar oxygen tension in babies breathing 15% oxygen studied by Cross et al. (1958) was 44 mm. Hg.

These calculated values might imply that babies were suffering from central respiratory depression, and in air the minute volume was in the low range of normal (442 mls/min.). However the babies had not been given any sedation and there is no collateral evidence to support this hypothesis.

Possibility of Rebreathing. The other possibility is that a certain amount of rebreathing was taking place, but had this been so, one would have expected hyperventilation. One possible explanation of the absence of ventilatory response to the hypercapnia might be the apparent simultaneous hypoxia.

TABLE 17

ALVEOLAR O_2 AND CO_2 TENSIONS (p. alv. O_2 p. alv. CO_2)

IN THE WORK OF CROSS ET AL. (1958) COMPARED WITH THOSE FOUND BY OTHER WORKERS; mm Hg. BTPS.

			Cross et al. (1958)	Nelson, Prod'hom, Cherry, Lipsitz & Smith (1962)	PET	Strang (1961)
Breathing air:	p.alv.O_2	(BTPS)	74	110	O_2	110
	p.alv.CO_2	"	60	31	CO_2	33
Breathing 15% O_2:	p.alv.O_2	"	44	-	-	
	p.alvCO_2	"	54	-	-	

Pet O_2, Pet CO_2 = End tidal oxygen and carbon dioxide partial pressures.

BTPS = body temperature, atmospheric pressure, saturated with water vapour.

The following formula was used to calculate p.alv.O_2 and a similar one to calculate p.alv.CO_2.

$$(V_T - V_D) \times \%\ O_2 \text{ alv. air (BTPS)} = \left(V_T \times \%\ O_2 \text{ exp.air dry NTP} \times \left(\frac{713}{760}\right)\right) - \left(V_D \%\ O_2 \text{ (atmos. air)} \times \left(\frac{713}{760}\right)\right)$$

where V_T = Tidal volume,
V_D = Physiological dead space } mls, BTPS
V_A = Volume of alveolar air

and V_T = minute volume (mls, BTPS) ÷ respiratory rate/min (f) and

$$\text{p.alv.}O_2 = \frac{\%\ O_2 \text{ alveolar air}}{100} \times 713$$

TABLE 17 (cont'd).

and

$$p.alv.CO_2 = \frac{\%\ CO_2 \text{ alveolar air}}{100} \times 713$$

The following values were substituted:

		Minute volume mls/min BTPS	% O_2 exp. air dry NTP	% CO_2 exp. air dry NTP	
Air	Period 1	442	14.53	5.13	
15% O_2	Period 2	451	9.55	4.70	Table 2 Cross et al. (1958)

assuming

f = respiratory rate = 31/min (Table 3 Cross et al. 1957)

Although published a year earlier the work of Cross et al. (1957) was done at the same time, in the same apparatus, and by the same investigators as the work with 15% oxygen. V_D = physiological dead space = 5.6 mls BTPS; this value was obtained from the mean of the results for full term normal infants of Cook, Cherry, O'Brien, Karlberg and Smith (1955) (mean V_D (n = 10) 5.7 mls BTPS and mean weight 3.02 Kg) and Nelson et al. (1962) (mean V_D (n = 8) = 5.4 mls BTPS and mean weight 3.36 Kg). The results combined give a mean V_D of 5.56 mls BTPS (taken as 5.6 mls) and a mean weight of 3.17 Kg. which is sufficiently close to the mean weight, at the time of examination, of the infants studied by Cross et al. (1958) Table 2 of 3.11 Kg.

Strang (1961) found by plotting the expired CO_2 and N_2 concentrations against the expired volumes that the dead space was 8-9 mls in mature babies of about 3 Kg. If these values are used the $p.alv.O_2$ is even lower and the $p.alv.CO_2$ even higher. Even when the calculation is basal on a dead space value of nil the values for $p.alv.O_2$ and the $p.alv.CO_2$ are still slightly abnormal:

$p.alvO_2$ = 104 mm Hg., $p.alv.CO_2$ = 37 mm Hg.

Discussion (cont'd).

The effects of simultaneous hypoxia and hypercapnia have been examined in detail (Cross, Hooper and Lord, 1954). Babies breathing a mixture of 15% oxygen and 2% carbon dioxide in nitrogen were found to have a minute volume 50% greater than when breathing air, which suggests that the subjects of the work on 15% oxygen and metabolism (Cross et al. 1958) should have been capable of some increase in minute volume. But as already stated the minute volume was normal.

Further in the initial stages of the experiments of Cross et al. (1958), at the beginning of any rebreathing, one would expect a rise in arterial pCO_2 capable of causing an increase in minute volume before the depressant effects, if any, of hypoxia became evident. A rise in p Alv. CO_2 of 10 mm. Hg. causes a rise in pulmonary ventilation per minute of about 1 litre, (calculated from Avery, Chemick, Dutton and Solbert, 1963). The continuous record of V.min. showed no such change, and was normal throughout.

Avery et al. (1963) noted that the ventilatory response diminished after infants had a p Alv. CO_2 of 50-60 mm. for 5 mins., but there was no evidence of any diminished ventilation in the original experiments of Cross et al. (1958).

The authors were well aware of the difficulties that would accompany rebreathing and made tests which indicated that it was unlikely. Although one cannot come to a very definite conclusion, the absence of direct evidence strongly suggests that rebreathing did not occur while the babies breathed air. Rebreathing in 15% oxygen when the apparatus and flow rates were similar, appears equally unlikely. Examination of the original experimental protocols (Cross et al. 1958)

Discussion (cont'd).

shows the mean flow rate in air was 1848 mls/min. (N.T.P.) and in 15% oxygen 1713 mls/min. (N.T.P.). There is no statistically significant difference between these values. ($t = 2.0$; at 29 degrees of freedom and $p = 0.10$, $t = 1.70$: at $p = 0.05$, $t = 2.04$, i.e. 0.10 greater than p greater than 0.05). Thus the discrepancy between the original and the present findings cannot be explained on the hypothesis that the babies were more severely hypoxic than expected when breathing 15% oxygen.

Moreover it can be calculated (Appendix 3) that the gas speed was of the order of 6 cm/second and this alone suggests that rebreathing was unlikely .

No explanation can at present be offered for the abnormal p Alv. O_2 and p Alv CO_2 values obtained by calculation from the original data. Whatever their explanation it does not seem correct to attribute the fall in oxygen consumption in 15% oxygen to this cause.

Environmental temperature in the work of Cross et al. (1958).

When Cross, Tizard and Trythall performed their pioneer work in 1955 (reported in 1958) on the effect of 15% oxygen, the marked sensitivity of the newborn infant to relatively small changes in environmental temperature (compared with the changes needed to evoke a metabolic response to cold in adults), was unknown. Not until the work of Brück (1961) were the effects of apparently minor changes in the skin temperature fully appreciated and only in recent years has the importance of the facial skin in regulating heat production been documented (Mestyán, 1964). In 1959 Cross noted that the environmental temperature of the infants studied by him and his colleagues was not known and that the

Discussion (cont'd).

metabolism of hypoxic infants would have to be reinvestigated with strict control of environmental temperature. Although the exact environmental temperature was not known it has been possible to obtain room temperatures from the original experimental protocols, and outside air temperatures from the Meterological Office.

As the suggested explanation of the discrepancy between our work and that of Cross et al. (1958) depends on present day concepts of temperature regulation, it is necessary to digress in order to attempt to outline briefly the modern theories of temperature control.

It will then be suggested that the cool air applied to the facial skin of the infants studied by Cross et al. (1958) stimulated an increase in oxygen consumption and that the removal of this stimulus and its replacement by warmer 15% oxygen caused the oxygen consumption to fall.

It is not suggested that the cold air on the face lowered the deep body temperature and stimulated oxygen consumption but that the facial skin is sensitive to cold stimuli and that cooling the face alone evoked a metabolic response to cold.

Discussion (cont'd).

CONCEPTS OF TEMPERATURE REGULATION.

The importance of peripheral temperature receptors in adult man, animals and newborn infants will be discussed first, and then the role of facial skin in regulating heat production. There is ample evidence of peripheral cold receptors in adults, (Hardy, 1961) and recently much evidence has accrued to show that oxygen consumption of newborn infants in the cool is likewise controlled by peripheral skin thermal receptors, (Adamsons et al. 1965; Hill and Rahimtulla, 1965).

The suggestion that cooling the facial skin evokes metabolic response to cold implies that:-

1. Oxygen consumption and metabolic response to cold are influenced by peripheral temperature receptors.

2. That facial skin plays a role in temperature regulation.

To put this concept into perspective it is necessary to outline the current views of regulation of temperature and metabolic response to cold. Three excellent reviews have appeared on this topic, those of Hensel (1959), Hardy (1961) and Hemingway (1963), and much of the present account is taken from them.

Although Sherrington (1924) thought that changes in deep body temperature were responsible for the initiation of shivering and according to Davis and Mayer (1955) most text books until that date have emphasised exclusively the role of body temperature, it is now evident that peripheral receptors are the most important in initiating the metabolic response to cold.

According to Hardy (1961), "It seems clear that in the cold the thermoregulatory drive originates in the periphery and the elevation of body temperature is

Discussion (cont'd).

likely to be due to the vasoconstriction and increasing metabolism evoked by the strong phasic responses in the skin and respiratory tract by falling temperature." There is ample evidence to support this view. Hemingway (1963) concluded similarly that the peripheral receptors form the main regulatory control for shivering and suggested that fine control is provided by peripheral receptors with a coarse emergency control exerted by central mechanisms.

Evidence for Peripheral Receptors in Adults.

There are many experiments which demonstrate a rapid onset of shivering in the cold without any drop and often with a slight increase in rectal temperature, (Jung, Doupe and Arnold, 1937, men; Davis and Mayer, 1955, rats; Horvath, Spurr, Hutt and Hamilton, 1956, men; Spurr, Hutt and Horvath, 1957, men; Good and Sellers, 1957 a & b, dogs; Ogata, Sasaki, Murakami, Watnabe, Kori and Yagi, 1958, men).

The exposure of the peripheral receptors to warmth will inhibit shivering in the presence of low deep body temperature as Davis and Mayer (1955) showed. When shivering rats were heated with infra red radiation shivering stopped, with a mean rise in skin temperature of 4.3°C, although the rise in rectal temperature was only 0.1°C from 36.3°C.

In the less elaborate but convincing work of Barcroft (1937) shivering stopped when blankets were applied to men who had been exposed to cold air, 5°C, even though rectal temperature was about 1°C below control levels. Jung et al. (1937) reached a similar conclusion.

Discussion (cont'd).

It is clear that all these workers considered the peripheral thermoreceptors responsible for the initiation of the metabolic response to cold. Hensel (1959) noted that in the experiments mentioned above the hypothalamic temperature had not been recorded directly and the experiments were "not conclusive as yet". He added that it seemed unlikely that a drop in hypothalamic temperature had occurred. The work of Brendel (1960) is important in this respect. The head and body of a dog were separately perfused. When the temperature of the blood to the brain was lowered and the skin temperature kept normal, oxygen consumption was not increased. But when the head was perfused with blood at a normal temperature and the skin temperature lowered, oxygen consumption increased 2.8 times the value in the warm. The work of Hallwachs, Thauer and Usinger (1961) permits a similar conclusion.

This does not deny the deep or central temperature receptors have a role of lesser importance in the metabolic response to cold (cf. Freeman and Davis, 1959, cats; Fusco, Hardy and Hammel, 1961 and Hammell, Hardy and Fusco, 1960, dogs; Mestyán, 1964, newborn rabbits).

Hensel (195?) suggested that temperature regulation is controlled by cutaneous receptors with the central control consisting of a change of sensitivity.

None of the work quoted above applies directly to the human infant but there is much recent evidence to show that metabolic response to cold is controlled by similar factors. It must be born in mind that in

Discussion (cont'd).

babies and in other newborn animals shivering is a very late manifestation of the metabolic response to cold which is perhaps better judged by the increase in oxygen consumption.

Importance of Peripheral Receptors in Infants.

The figure shown at the beginning of the results section (Fig. 20) demonstrates that oxygen consumption can be increased in cooler air before the rectal temperature has fallen. It was pointed out that the oxygen consumption bore no apparent relationship to the level of rectal temperature or to whether it was rising or falling. These observations are in agreement with those of Hill and Rahimtulla (1965) who found that cold produced an increase and warmth a decrease in heat production which was "immediate and apparent long before there had been time for a change in body temperature." Figs. 27a, b, c, d, e in the results section of this thesis show the rapid changes in rectal temperature which took place while oxygen consumption remained constant.

Brück (1961) found that "except on the first day of life metabolic rises regularly occur without a previous drop in body temperature. Thus we may assume that the rises are caused entirely by changes in skin temperature, i.e. via the cutaneous thermal receptors." In infants of all ages oxygen consumption on rewarming rapidly fell before there was any increase in body temperature even if the latter had decreased considerably.

Mestyán, Varga, Fohl and Heim (1962) and Mestyan, Fekete, Bata and Jarai (1964), Levison and Swyer (1964) Adamsons et al. (1965) and Hill and Rahimtulla (1965) showed that oxygen consumption is not related to rectal temperature in the cool or in the warm. The present

Discussion (cont'd).

work has already been noted to show that rectal temperature does not affect oxygen consumption in the warm and that oxygen consumption is constant in the warm inspite of a rapidly rising rectal temperature. (Mestyán et al. (1964) have suggested that the constancy of metabolic rate at different rectal temperatures while the baby is exposed to a neutral temperature can only be explained by the assumption that after exposure within the neutral range the skin temperature soon reaches the critical level at which heat production falls to the minimum value).

Brück (1961) examined the quantitative relationship between average skin temperature and heat production and found that in newborn infants lowering of the average skin temperature from about 37°C at ambient temperature 32°C to about 35-36°C at an environmental temperature of 28°C in his apparatus, was sufficient to produce and maintain a metabolic rise and to cause a marked lowering in the skin blood flow in the heel, (Fig. 8 and Table 2, Brück (1961)). The average skin temperatures found by Day (1943) at ambient temperatures of 32 and 28°C were about 1°C lower than those of Brück (1961) but it must be remembered that the methods of calculating the average skin temperature were slightly different, that the same environmental temperature in different apparatus may not represent the same cold (or warm) stress, and that Day was working with premature infants. (See Chart 8, Day (1943)).

Adolf and Molnar (1946) showed that the skin temperature of adults at 26-28°C, their neutral temperature range, is only 32-33°C and a rise in heat production corresponding to that in the infant did not

Discussion (cont'd).

take place until the skin temperature has been lowered to less than 30°C. Calculations from the data of Adolf and Mclnar (1946) show that in adult man a fall in skin temperature of 1°C is associated with an increase in oxygen consumption of about 0.75 mls/min/Kg. while calculations from Brück (1961) show that a 1°C fall in skin temperature in a baby is associated with an increase in oxygen consumption of no less than 4.6 mls/min/Kg.

Levison and Swyer (1964) and Adamsons et al. (1965) have both found a marked correlation between fall in skin temperature and increase in oxygen consumption. It can be calculated from the data of Adamsons et al. (1965) that a fall in skin temperature of about 1°C produced an increase in oxygen consumption of about 3.3 mls/min/Kg. They also confirmed that the threshold skin temperature for increasing oxygen consumption was about 35-36°C. The skin temperature measured was that of the anterior abdominal wall which is higher than the average skin temperature. Levison and Swyer (1964) came to a similar conclusion.

Mestyán et al. (1964) studied the relation of skin to deep body temperature in the metabolic response to cold of hypothermic premature infants exposed naked to room temperatures varying between 22-25°C. They concluded that the fall in oxygen consumption was more closely related to skin temperature than to colonic temperature. Their observations on the effect of altering the skin temperature of naked hypothermic infants at a constant cool environmental temperature, 25°C, are the most relevant for the present purposes. By infra red radiation the temperature of the skin of the abdomen and thorax was slightly increased. The rise in skin temperature caused a sharp fall in oxygen consumption which occurred before the temperature of the skin reached that of the colon and continued while

Discussion (cont'd).

the skin rose above colonic temperature. Nearly all the fall in oxygen consumption took place while the rectal temperature was itself falling, the opposite to what one would expect of the deep body temperature controlled oxygen consumption.

It appears that in infants as in adults skin temperature is of far more importance than rectal temperature in regulating oxygen consumption in the cool. In all the experiments above the infants were naked and stimuli were not applied to the facial skin alone. However there is much evidence to show that the facial skin is sensitive to heat and cold.

THE IMPORTANCE OF THE FACIAL AREA AND RESPIRATORY TRACT IN HEAT REGULATION.

This will be discussed in relation to adult man and animals and then in relation to infants.

In adult man and animals.

There is no doubt that the facial skin is highly sensitive to changes in temperature. The whole body has been charted for thermo sensitive spots, which are divided into hot and cold sensitive types, by many authors particularly Stughold and Porz (1931). Zotterman (1959) reviewing this work and others showed that the highest density of thermo sensitive spots is found in some areas of the face particularly the lips, nose and eyes. The lips contain 16-19 cold spots per sq. cm., the nose 8-13 cold spots per sq. cm., compared with the maximum elsewhere in the body, 8-12 per sq. cm. on the abdomen.

The forehead too is very cold sensitive but only moderately sensitive to warmth. In mammals cold sensitivity appears to be situated particularly on the bare parts of the nose and of the tip of the tongue.

Discussion (cont'd).

According to Hensell (1959) it is generally agreed that cold receptors in the tongue exhibit a steady discharge frequency that depends on absolute temperature.

Hardy et al. (1937) investigated the effect of infra red radiation on various parts of the body using a radiation thermopile and determined the minimum amount needed to promote a sensation of warmth. The facial skin was found to be more than twice as sensitive for warmth per unit area as the back of the hands, which was the most sensitive part of the rest of the body, and a rise in facial skin temperature of 0.009°C in the area of a few square centimetres was always felt within 3 seconds.

Hensell (1959) noted that the trigeminal area in the cat was very sensitive to warmth. Zotterman (1959) mentioned that the high sensitivity of the trigeminal area which in man is directly exposed in all weathers no doubt has special significance.

The high sensitivity of the trigeminal area may be related to the large amount of heat loss from the head in the cold. Froese and Burton (1957) found that there was little or no vasoconstriction in the head in response to cold, both when cold stimuli came from the head alone or from the rest of the body as well. The insulation of the tissues of the head was constant and did not change with the external temperature. Because of the absence of vasoconstriction as much as 50% of the heat loss may be from the head in a clothed man with no head gear in a cold environment. Koenig (1943) found that iced water applied to the forehead of adult man in a warm environment immediately elevated the rate of oxygen consumption to values 60% greater than in control periods. No other part of the body was so sensitive.

Discussion (cont'd).

Bader and Macht (1948) mentioned that German workers in World War II had obtained unpublished evidence that the face is a reflexogenic zone and showed that heating the face of adult man in the cold with infra red was a more powerful stimulus in producing reflex vasodilatation than the same stimulus applied elsewhere in the body. Hardy (1950) commented that "the importance of the face as an exposed thermosensitive area in the thermoregulatory adjustments of the clothed man is apparent from this study."

Rein (1940) thought that the face had a special role as a reflexogenic area. In the adult dog cooling of the skin of the nose and face increased the blood flow through the carotid artery by 40%. He also showed that cooling the dog's nose increased the heat loss from the hind leg. Cooling the nose of the cat provokes an increase in liver temperature within seconds (Jitariu, Koch and Otto, 1942).

The role of facial skin is also indicated by the work of Chattonet and Tanche (1956) who investigated the importance of rectal and peripheral temperature in dogs with spinal transections in the cervical region. When the trigeminal nerve was anaethetised locally shivering was induced by cooling the lower part of the body to a rectal temperature of 36°C. But without paralysis of the trigeminal shivering was induced by cooling the skin of the head to 33°C.

Role of the facial skin in babies.

The simple fact must be borne in mind that the head is very much bigger in proportion in a baby than in an adult. It can be calculated (from Nelson, 1964) that in a baby the face occupies about 21% of the body surface

Discussion (cont'd).

seen from the front whereas in an adult the face occupies only about 5% of the body surface similarly seen. This means that in an infant with the face projecting from the body plethysmograph (Cross, 1949) much more of the whole body surface would be exposed than in an adult similarly positioned. As Froese and Burton (1957) have pointed out that 50% of the heat lost from the clothed body in the cold is from the head, it is conceivable that the heat losses from the exposed face in the body plethysmograph might be greater than one would initially suspect.

Brodie, Cross and Lomer (1957) calculated that in the body plethysmograph the exposed area of the face was about 2.5-3% of the whole body surface of the infant and that the heat loss from the face and through the breath was about 13% of the total heat loss.

Babies have been successfully swaddled from time immemorial and this historical fact deserves to be mentioned.

Experiments in our apparatus have shown that clothed babies respond to a lowering of the environmental temperature as rapidly as do naked babies although only the face and head are exposed. The increase in oxygen consumption was observed when the environmental temperature was lowered to about 26°C to 28°C.

Brück (1961) showed that vascular reactions in full term and premature infants can be produced merely by a local cooling or warming of the face accompanied by only slight opposite changes in body temperature. Infra red irradiation of the face produced an increase in forehead temperature, and the skin blood flow in the heel increased to approximately double the value found in the control period. The skin blood flow fell rapidly

Discussion (cont'd).

to control values about 2 minutes after radiation was discontinued. Not only was the facial skin sensitive to infra red radiation but if the face was heated by a current of warm air a similar increase in skin blood flow in the heel resulted. Lastly but most important for the present purposes when the heater was switched off and cold air was used the forehead skin temperature and the heel blood flow rapidly fell. A normal body temperature 36.5°C to 37.5°C, was necessary for the demonstration of these vascular reflexes.

Seraphin (1955) produced similar vasomotor responses by facial cooling or warming in the human neonate, and it is interesting that he drew attention to the greater relative facial area in infants.

Facial skin temperature and oxygen consumption in babies.

Shortly after this suggestion that cold air or warm 15% oxygen might be important in the work of Cross et al. (1958), Mestyán, Jarai, Bata and Fekete (1964a) published an important paper on the significance of facial skin temperature in regulating heat production in premature infants. The introductory paragraph is very relevant to the suggestion that cold air on the face might increase oxygen consumption. "In a previous study (Mestyán, Fekete, Bata and Jarai, 1964b) concerning the energy metabolism of premature infants wrapped in swaddling clothes and exposed to a room temperature of 20°C to 22°C heat production was found to be definitely higher than that obtained in the naked state at 35°C to 36°C. Since under these conditions the temperature of the clothed body surface seemed unlikely to account for the increased oxygen consumption, the possibility has been raised that cooling the uncovered face and head

Discussion (cont'd).

exposed to 20°C to 22°C might evoke a metabolic response to cold. The same suggestion concerning the possible role of the facial skin in chemical heat regulation of clothed infants was recently made by Pribylova." Pribylova and Znamenàcĕk (1964) found that in lightly swaddled infants exposed to room temperature (19°C) the skin temperature fell only in the extremities but not on the abdomen or forehead.

This paragraph of Mestyán et al. (1964a) has been quoted in full because it illustrates almost exactly the same concept from two completely independent investigators. The only differences appear to be that in the body plethysmograph (Cross, 1949) the head was not exposed but only the face and that it is suggested that the temperature of the air in contact with the face was considerably less than 19°C to 22°C.

In the work of Mestyán et al. (1964a) premature infants were wrapped in swaddling clothes and exposed to room temperature. The temperature within the swaddling clothes, the deep body temperature and the abdominal skin temperature were determined, and oxygen consumption was measured. The effect of thermal stimuli on the face was demonstrated by applying radiant heat or by placing of a double walled metal plate, through which cold water was run, 5 to 8 cm. from the face.

The mean oxygen consumption when the forehead was exposed to room air was about 27% above basal levels. When the forehead was heated the oxygen consumption fell to basal levels. After the heating was switched off the oxygen consumption rose to the previous level.

Discussion (cont'd).

The changes in the rectal temperature and in the temperature within the swaddling clothes were very small and not statistically significant. From this work it seems probable that the fact that the face was uncovered contributed to maintaining the oxygen consumption at values about 27% above the basal level.

In further experiments the facial skin was cooled by running cold water through the metal plate described. In all these infants a drop in forehead temperature was held to cause a considerable increase in oxygen consumption (mean increase 37%). When cooling was discontinued the oxygen consumption fell to control values. There was virtually no change in abdominal skin temperature or rectal temperatures.

Shortly after the fall in forehead temperature, movements and increasing restlessness accompanied the increase in oxygen consumption. The fluctuations in oxygen consumption followed closely the intensity of the muscular activity. This suggests that the increase in oxygen consumption was due to the activity. However the fact that the exposure of the faces and heads of the infants to room temperature appeared to maintain oxygen consumption 27% above the basal level indicates that the stimulation of oxygen consumption by cool facial skin temperatures need not be accompanied by activity.

Mestyán et al. concluded that cooling the uncovered face and head should be regarded as an important stimulus invoking chemical heat production.

Conclusion. In babies whose faces were exposed to room air infra red radiation on the face lowered oxygen consumption by 27% and cooling the face increased oxygen consumption by 37%. In this context a concept

Discussion (cont'd).

that cooling the face only would increase oxygen consumption by 17% appears entirely acceptable. This is the explanation that will be put forward to explain the fall in oxygen consumption in 15% oxygen observed by Cross et al. (1958).

Temperature receptors in the respiratory tract.

Temperature receptors exist not only in the facial skin but also in the respiratory tract. Cort and McCance (1953) observed that in intact conscious piglets in the cool there was a convulsive shiver with each inspiration but that during expiration there was no shivering. They quoted similar observations in puppies and designed a preparation to confirm these observations.

Piglets aged 3 to 6 weeks (3-6 Kg.) were lightly anaethetised and the tracheae cannulated. Warm air at 40°C, (the normal pig rectal temperature is 40°C), room air or air at 4°C were passed through the cannula. It was observed that the change from warm air to room or cold air precipitated rhythmic shivering usually at the next inspiration. They postulated the existence of temperature receptors in the walls of the trachea and bronchi and showed that afferents were in the vagus. They pointed out that since respiratory shivering is so obvious in the young unaesthetised animal and usually absent in the adult it may well be that the young animal is unable to warm the inspired air to body temperature as well as the adult.

Barcroft (1934) observed that shivering always occurred on the inspiratory phase of respiration "suggesting that shivering causes inspiration or inspiration of cold air causes shivering, the latter being more likely." Hemingway, Forgrave and Birzis, (1954) noted that shivering occurred on inspiration

Discussion (cont'd).

in cats and Blatteis (1964) found the same in dogs.

The fact that shivering is associated with inspiration suggests either that there must be temperature receptors at sites higher in the respiratory tract than the trachea and bronchi, (for in these areas the inspired gas has already been warmed to body temperature, Cole, 1953) or that there is a central mechanism of facilitation between shivering and inspiration.

Effect of high humidity.

Adult man. Burton, Snyder and Leach (1955) demonstrated that adult man showed a much greater metabolic response in dry cold than in damp cold. They showed that shivering, sensation of cold and rise in rectal temperature were much more marked on exposure to dry cold (relative humidity (R.H.) 30%) than on exposure to damp cold air, (80% R.H.). Wind speed was the same in both dry and damp cold air.

Infants. In infants also there is evidence for the effect of humidity on metabolic response to cold. Silverman and Blanc (1957) reported that the rectal temperature of premature infants was significantly greater when they were placed in an atmosphere of 90% Relative Humidity than in the more moderate humidity of 30-60 R.H., although the air temperature was the same (mean 28.9°C). In a further trial when the effect of the same range of humidity was studied and the skin temperature of the anterior abdominal wall was maintained constant by infra red radiation, it was found that high humidity reduced the amount of radiation necessary to maintain a constant skin temperature (Silverman, Agate and Fertig, 1963).

Discussion (cont'd).

It is clear that the high humidity reduced the heat loss. However the work done above was concerned with the effects of humidity on the whole body surface and not on the facial skin alone.

EXPLANATION OF DISCREPANCY BETWEEN PRESENT AND ORIGINAL WORK.

The suggested explanation for some of the findings of Oliver and Karlberg (1963) and for the discrepancy between this work and that of Cross et al. (1958) lies in the fact that the newborn infant responds with a rapid and appropriate increase in oxygen consumption when the temperature of the surrounding gas is lowered, and conversely when it is raised, (Brück, 1961; Hill and Rahimtulla, 1965).

In both the original work (Cross et al. 1958) and that of Oliver and Karlberg (1963), the experimental procedure was similar. In a preliminary set of experiments the oxygen consumption of a baby was measured while it was breathing air, and a second measurement was made again in air a few minutes later to establish the reproducibility of the method (Series I). At a later date and in another group of babies, the oxygen consumption while breathing air was compared with that while breathing 15% oxygen a short time afterwards (Series II).

Analysis of earlier data.

The data were statistically analysed so as to compare the means by t tests as in Figs. 48 and 49. For the t test to be valid the values must be normally distributed (this is shown in Figs. 50 and 51).

The most obvious finding is that in both studies the mean oxygen consumption in air before 15% oxygen

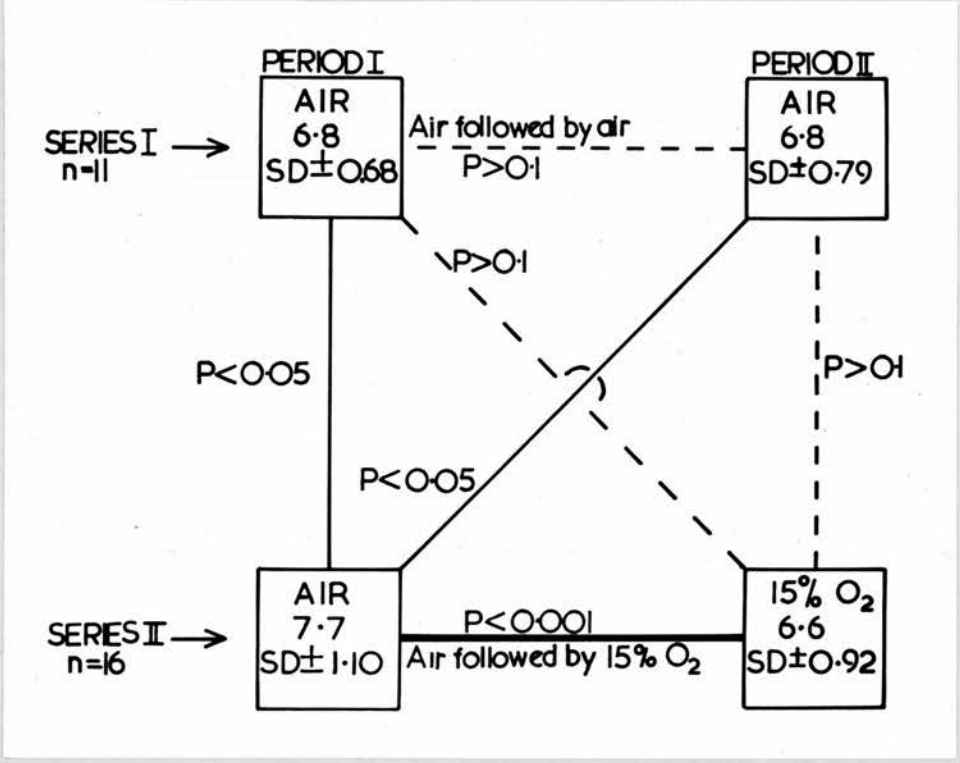


Fig. 48. Data of Cross et al. (1958) (Tables 1 and 2); clothed newborn babies breathing either air or 15% oxygen. In each box is shown the composition of the gas breathed and the mean oxygen consumption in ml/min. Kg. ± SD. The means have been compared in pairs by a t-test. A solid line indicates a significant difference between the means, while a pecked line indicates an insignificant difference. For further explanation see text.

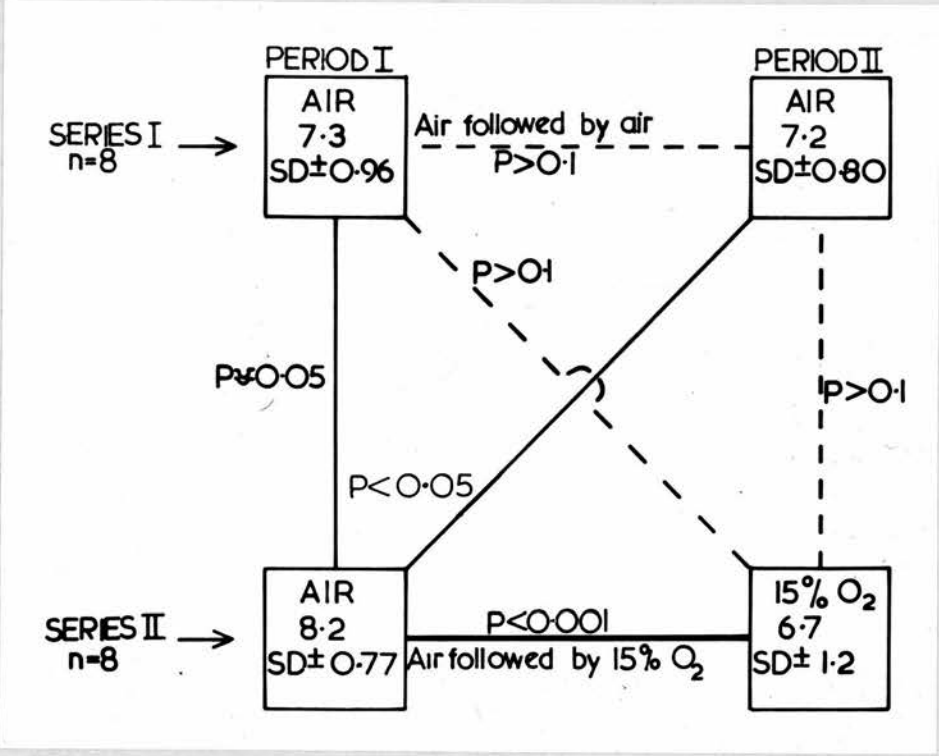


Fig. 49. Data of Oliver and Karlberg (1963) (Table 1); clothed newborn babies in the cool breathing either air or 15% oxygen. Other details as given in caption to Fig. 48.

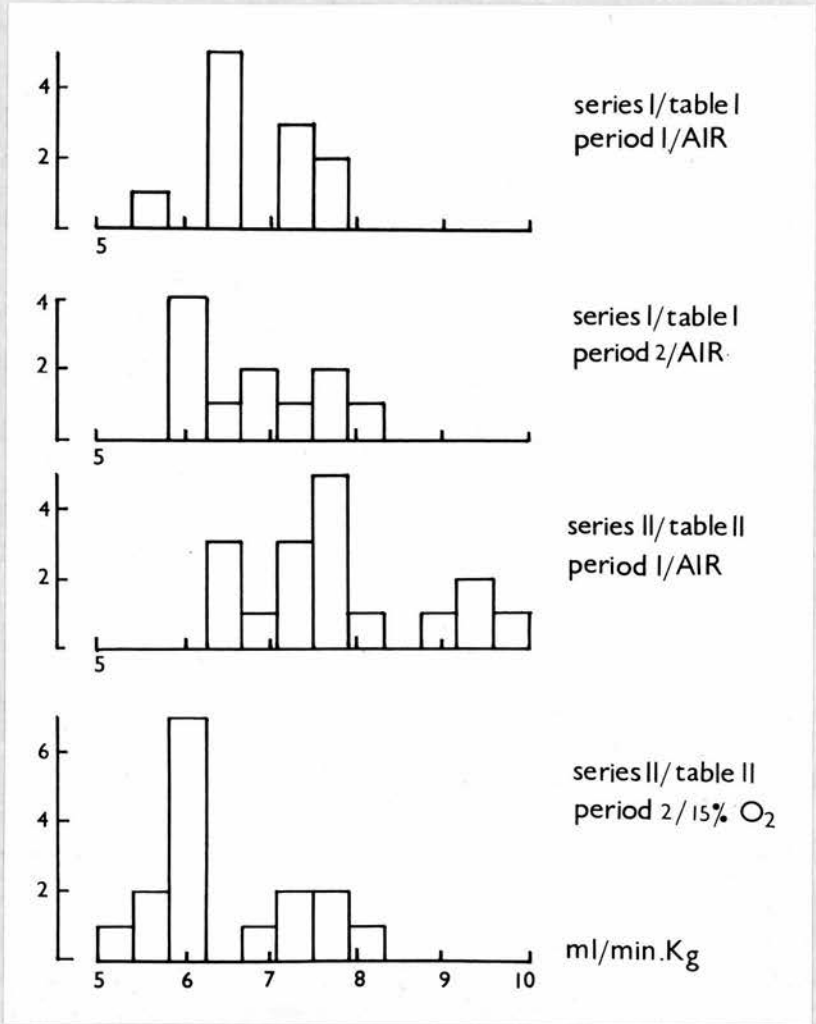


Fig. 50. Frequency distributions of measurements of oxygen consumption. From Tables 1 and 2, Cross, Tizard and Trythall (1958).

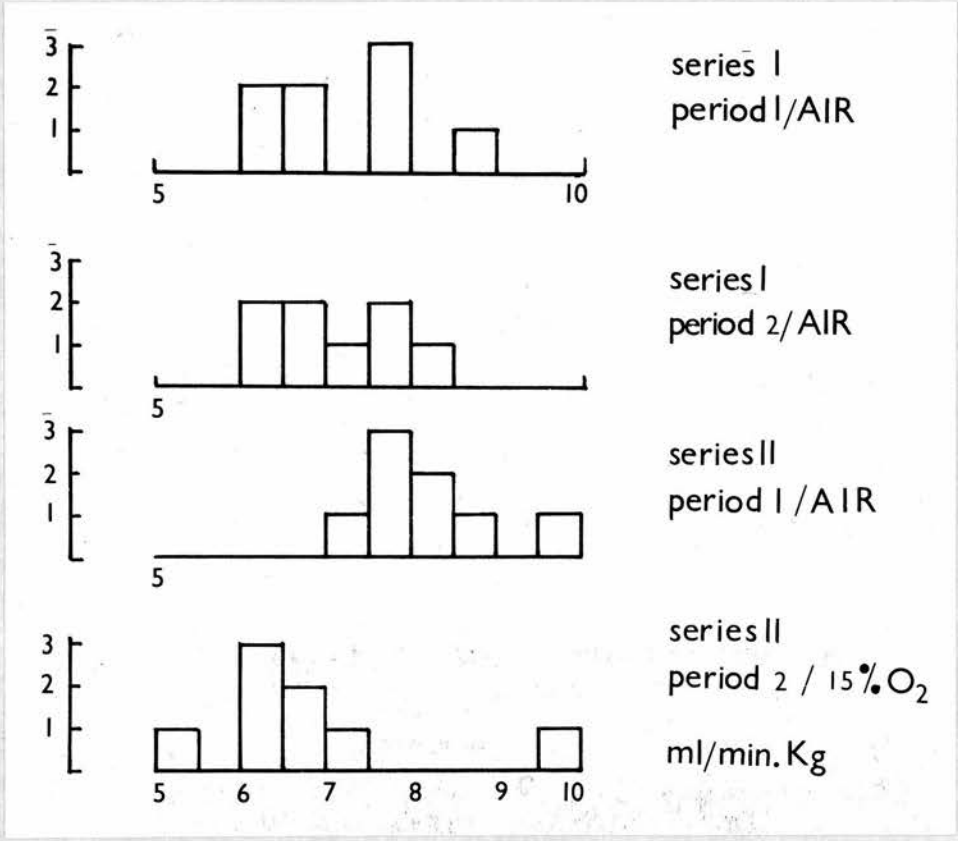


Fig. 51. Frequency distributions of measurements of oxygen consumption, from table 1 parts 3 and 4, Oliver and Karlberg (1963).

Discussion (cont'd).

is significantly greater than that in the other periods and not as might be expected that the mean oxygen consumption in 15% oxygen is significantly less than in the other 3 periods. For the purposes of the following discussion this conclusion can be subdivided into:-

1. The oxygen consumption in air before 15% oxygen (in Series II) was significantly greater than in the air——air control periods (Series I).

2. The oxygen consumption fell significantly when 15% oxygen was given after air.

In fact in neither study is there a significant difference between the mean oxygen consumption when breathing 15% oxygen and that when breathing air in the control periods. The proposed explanations for the two conclusions above will be discussed in the order given.

Explanation of greater oxygen consumption in Series I

The work of Oliver and Karlberg, 1963.

In the experiments of Oliver and Karlberg (1963) the recorded environmental temperature was the temperature of a lucite hood extending to about hip level which was closed at the foot end by wrapping thin plastic sheeting around the knees. The lower legs and feet were excluded from the apparatus and were kept covered by a blanket. The mean temperature of the hood was significantly lower in the experiments in which the baby was exposed to air, then 15% oxygen, than in those in which it was exposed to air only (see Table 18). It is suggested that the lower

TABLE 18

HOOD TEMPERATURES IN INFANTS BREATHING AIR FOLLOWED BY AIR (SERIES I) AND INFANTS BREATHING AIR FOLLOWED BY 15% OXYGEN (SERIES II) OLIVER AND KARLBERG, 1963.

	Mean Hood temp.	Significance of difference between means	Statistical data
Series I n = 8	26.1	$0.05 > P > 0.02$	At 13 degrees of freedom
Series II n = 7	24.2	($t = 2.34$)	($P = 0.05$ $t = 2.16$) ($P = 0.02$ $t = 2.65$)

In the two infants in which the hood temperature was not measured it has been assumed to be 2.5°C higher than the room temperature. (See authors' foot note).

Discussion (cont'd).

environmental temperatures caused the oxygen consumption in air before 15% oxygen to be greater than when air alone was given.

The work of Cross et al. 1958.

The similarity between the results of statistical analysis of both studies led to a re-examination of the temperature recordings in the work of Cross et al. (1958), which will be described as the original work. Two components must be considered which were not directly related to each other

1. The temperature of the air surrounding the baby who was clothed with a vest, and nightdress and wrapped in a thin sheet in the body plethysmograph.

2. The temperature of the gas breathed to which the face and upper respiratory passages were exposed.

Description of the Body Plethysmograph. The body plethysmograph (Cross, 1949) consists basically of a closed metal box which contains the infant's trunk and head and from which only the face protrudes. An inflatable pneumatic cuff encircles the bony parts of the face and head and seals the plethysmograph from room air. Changes in the volume of the box are recorded and are exactly equal to the volume of the gas breathed in or out. The air in the box is completely still apart from the relatively small to and fro movements caused by respiration. During the experiments with 15% oxygen the temperature of the air in the box was not measured but in a later series (Brodie et al. (1957), Fig. 3), it was shown to bear a constant relation to that of the room and to be about 4-5^{o}C greater.

Discussion (cont'd).

Role of room temperature. The room temperatures during the experiments are shown in Tables 19 (Series I) and 20 (Series II). The mean room temperatures in the "control" (Series I) and the air and 15% oxygen experiments (Series II) of the original work were very similar (Fig. 52), (21.7°C control, 20.4°C 15% oxygen experiments). If the two mean room temperatures are compared by a t test there is no statistically significant difference between them (t = 1.95, 0.1 greater than P greater than 0.05). The plethysmograph air temperatures in both series were therefore approximately 25°C.

It has been shown that the abdominal skin temperature of premature infants who were wrapped in swaddling clothes was about 36°C and only very slightly lower than the deep body temperature, when they were exposed to room temperatures of 20 to 22°C, (Mestyán, Jarai, Buta and Fekete, 1964). There are obvious but minor differences between the thermal environment of these babies and of those studied by Cross et al. (1958) but the results of Mestyán (1964) suggest that the skin temperature of the infants in the body plethysmograph was similar and hence was not likely to be a large stimulus to oxygen consumption. Celander (unpublished observations confirmed by Scopes (1966)) has also shown that the temperature inside the clothing of babies exposed to room temperature is of the order of 34-36°C.

Such skin temperatures are at about or above the level of the threshold for increasing oxygen consumption and would be expected to provide only a small stimulus to increasing oxygen consumption. The slightly cooler

TABLE 19

ROOM AND ATMOSPHERIC AIR TEMPERATURES, CROSS ET AL., 1958: INFANTS BREATHING AIR FOLLOWED BY AIR, (TABLE 1) (SERIES I).

No:	Date	Time	Oxygen consumption mls/Hour Kg. AIR Period 1	Period 2	Atmospheric air* Temperatures °C	Room Temperatures °C /
43	23-7-54	3 pm	441	481	18.9	22.3
44	26-7-54	12 noon	382	355	16.1	22.5
45	28-7-54	11 am	460	449	16.1	20.9
46	28-7-54	4 pm	336	355	16.7	21.9
47	29-7-54	3 pm	434	414	17.8	20.8
48	4-8-54	12 noon	383	411	21.1	23.5
49	16-8-54	4 pm	397	453	19.4	22.3
50	19-8-54	3 pm	469	471	12.2	19.9
51	24-8-54	3 pm	394	360	15.6	20.8
52	26-8-54	3 pm	377	370	19.4	21.5
53	9-9-54	3 pm	437	394	18.9	22.8
		Means	410	410	Means 17.5	21.7

* Data measured at the Meteorological Office, Kingsway, London, W.C.2.

/ Data obtained from experimental protocols.

TABLE 20

ROOM AND ATMOSPHERIC AIR TEMPERATURES, CROSS ET AL., 1958:
AIR AND 15% OXYGEN (TABLE 2) (SERIES 2)

No:	Date	Time	Oxygen consumption mls/Kg. Hr. Air	15% oxygen	Atmospheric* air temps. °C	Room / temps. °C
54	6- 9-54	3 pm	426	352	18.3	21.8
55	8- 9-54	12 noon	426	346	17.2	22.0
56	16- 9-54	11 am	488	401	17.8	20.8
57a	20- 9-54	3 pm	558	466	15.5	21.0
57b	27- 9-54	3 pm	525	460	13.9	20.2
58	4-10-54	3 pm	438	339	17.2	22.5
59	15-10-54	4 pm	379	330	15.5	22.4
60a	12-10-54	3 pm	452	428	11.7	20.0
60b	16-11-54	3 pm	554	426	10.0	18.0
61	18-11-54	3 pm	598	497	6.7	16.0
62	7-12-54	3 pm	469	372	4.4	16.5
63	8-12-54	4 pm	407	356	10.0	21.0
64	10-12-54	12 noon	470	357	7.2	18.0
65	20-12-54	3 pm	465	360	10.5	20.5
66	5-10-54	4 pm	380	305	17.8	22.5
67	18-10-54	4 pm	389	361	17.2	22.5
n = 16				Means	13.2	20.4

* Data measured at the Meteorological Office, Kingsway, London, W.C.2.

/ Data obtained from experimental protocols.

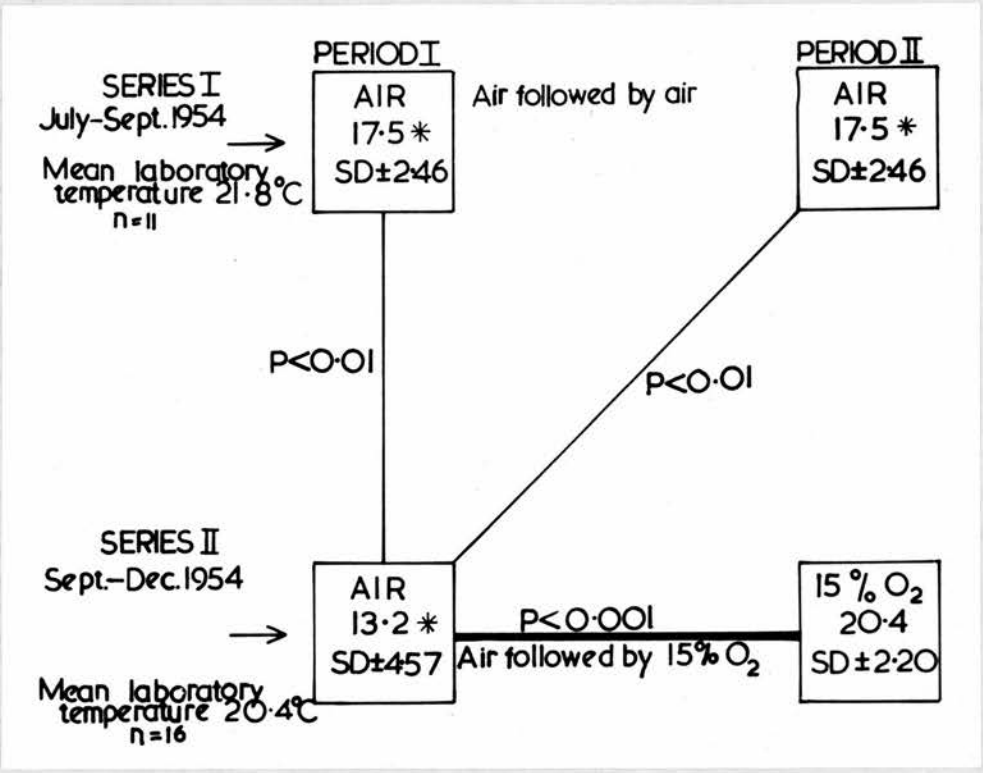


Fig. 52. Based on data obtained from a re-examination of the experimental protocols relating to Cross et al. (1958) together with values for outside air temperature in London at the time of each experiment (to the nearest hour) supplied by the Meteorological Office.

For each of the two series the time the experiments were performed, the number performed and the laboratory temperature (mean of all experiments) is given. In each box is shown the composition of the gas breathed and the mean presumptive temperature (outside air temperature) of the gas breathed in °C ± SD. The values marked by an asterisk are derived from Meteorological Office data for outside air temperatures; see text for further details.

Discussion (cont'd).

mean room temperature and hence mean plethysmograph temperature seems unlikely to have caused all change in oxygen consumption.

Role of outside air temperature. However in the original work the temperature of the air breathed during the air——air control periods was considerably greater than the temperature of the air breathed before the 15% oxygen, (see Tables 19 and 20). Throughout the work of Cross et al. (1957) and (1958) the air breathed was supplied from outside the building to ensure constancy of composition for analytical reasons. It was drawn through an opening in the wall and passed via a short length (about 2 feet) of wide bore, (3.5 cm.) tubing to the face mask; the temperature of the air, when it reached the infant, was probably not far above the temperature of the air outside the building and considerably lower than that of the room.

The actual atmospheric temperatures at the dates and the times of the experiments (to the nearest hour) have been obtained by courtesy of the Meteorological Office and it was fortunate that the temperatures were recorded not three miles from where the experiments were performed. The actual outside air temperatures obtained from the original data are shown in Table 19 (Series I) and Table 20 (Series II). The results of testing for the significance of the difference between the means are shown in Fig. 52. The differing outside air temperatures are accounted for by the fact that the air——air control experiments (Series I) were performed in the summer when the atmospheric air temperature was higher, but the air——15% oxygen experiments (Series II) were performed in winter.

Discussion (cont'd).

The mean temperature of the winter air was significantly less ($t = 2.84$, $0.01 > P > 0.001$).

Relation of outside air and room temperatures to oxygen consumption.

Both outside air and room temperatures correlate well with measurements of oxygen consumption in infants breathing air at different times of the year and this is shown in Figs. 53 and 54 in which the values for oxygen consumption obtained from Cross et al. (1958) Table 1 period 1 (Series I) and Table 2 period 1 (Series II) are plotted against the outside air (Fig.53) and room (Fig. 54) temperatures. In view of recent work on environmental temperatures the correlations are entirely acceptable. Both air and room temperatures correlate well with each other (Fig. 55).

Conclusion. The question arises of whether the cooler outside air or slightly lower room temperature or both was responsible for the significantly higher oxygen consumption in air in Series II. Although when both series are combined there is a better correlation of oxygen consumption with room than with outside air temperature, the mean room temperatures in Series I and II were not significantly different. On the other hand there was a highly significant difference between the mean outside air temperatures. One must also bear in mind the work which suggests that there would have been little change in skin temperature.

It is probable that the cooler air given before the 15% oxygen stimulated the face and upper respiratory passages and brought about a greater oxygen consumption than in the control experiments conducted in the warmer weather. This seems to be

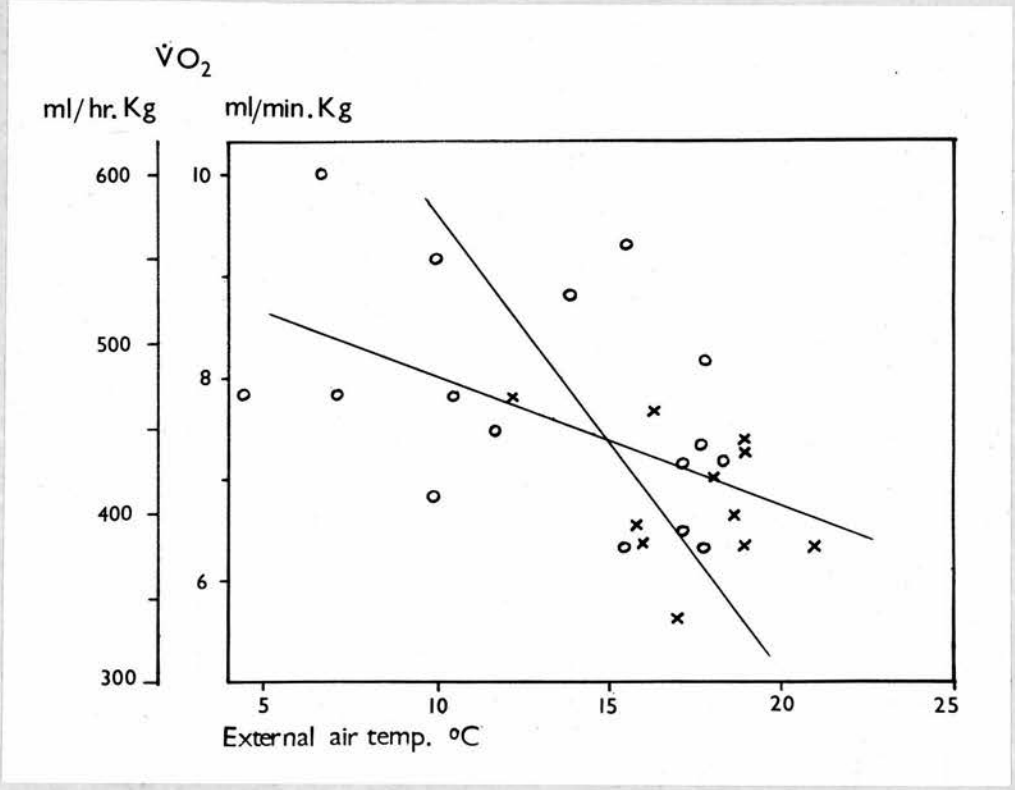


Fig. 53. Oxygen consumption ($\dot{V}O_2$) and outside air temperature (presumed temperature of gas breathed). From the data of Cross et al. (1958) Table 1 Period 1 (Series I) Symbol X, and Table 2 Period 1 (Series II) Symbol O. Correlation coefficient $r = -0.53$. $0.01 > P > 0.001$. Both regression lines are shown $x = -2.22y + 31.3$, $y = -0.126x + 9.25$.

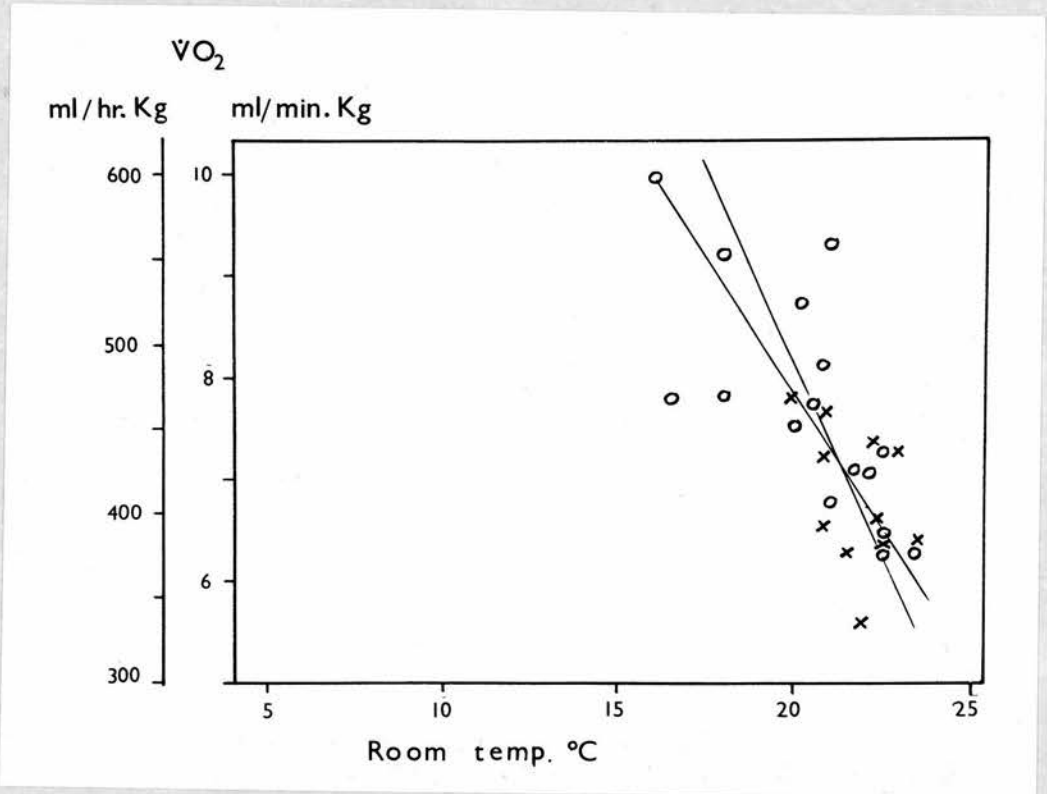


Fig. 54. Oxygen consumption ($\dot{V}O_2$) and room temperatures from the data of Cross et al. (1958). Table 1 Period 1 (Series I) Symbol X and Table 2 Period 1 (Series II) Symbol O. Room temperatures obtained from original data. Correlation coefficient, r, = -0.7 ($P<0.001$). Both regression lines are indicated.
$x = -1.299y + 30.53$
$y = -0.54x + 18.66$

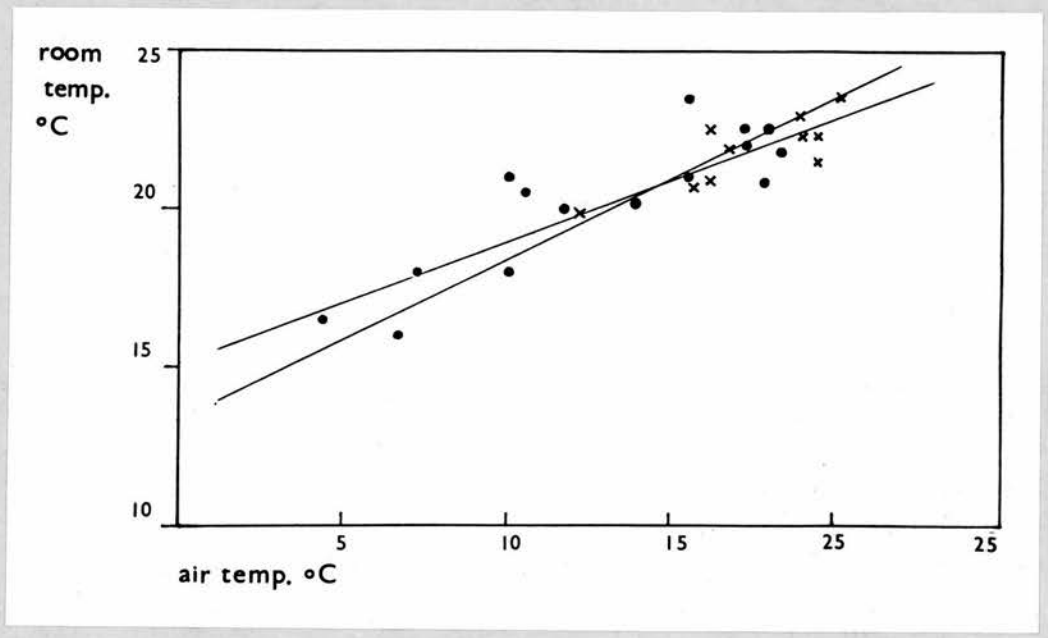


Fig. 55. Outside air and room temperatures at the times of measurements of oxygen consumption in Tables 1 and 2, Period 1, Cross, Tizard and Trythall (1958). Outside air temperatures from the Meteorological Office, room temperatures from original experimental data of Cross et al. (1958).
Correlation coefficient $r = 0.87$
Both regression lines are indicated.

$x = 1.97y - 26.26$

$y = 0.39x + 15.21$

Symbols: Table 1 Period 1 (Series I) X
Table 2 Period 1 (Series II) ●

Discussion (cont'd).

the main factor likely to have caused an increase in oxygen consumption, although the room temperature may have had some part to play. The amount of clothing and activity were the same, and the ages were not significantly different.

Explanation of fall in oxygen consumption in 15% oxygen

The work of Cross et al. 1958

The explanation offered for the fall in oxygen consumption in 15% oxygen depends on the fact that when 15% oxygen was given it was supplied from a balloon in the laboratory which had been filled before the experiment had begun from a cylinder via a humidifying bottle. It is highly likely that the temperature of the 15% oxygen was the same as that of the room. The mean room temperature was 20.4°C. Difference in gas temperatures. It follows that when the oxygen consumption in babies breathing outside air was compared with that in 15% oxygen there was a considerable difference between the temperature of the air and of the 15% oxygen. The mean temperature of the 15% oxygen (mean room temperature) was about 20.4°C, while the mean presumed temperature of the air breathed immediately before it was about 13°C. The difference between the mean room temperature and mean atmospheric temperature was highly significant ($t = 5.67$, $p < 0.001$). Because of this difference between the temperature of the air and the 15% oxygen the measurements of oxygen consumption when breathing cool air and warm 15% oxygen were not strictly comparable.

It has already been noted that the cooler air of Series II may have been a factor responsible for the

Discussion (cont'd).

oxygen consumption in air being about 15% greater than in Series I. When air and 15% oxygen were compared it is probable that the colder outside air applied to the face and upper respiratory tract caused oxygen consumption to be higher and that when warm 15% oxygen was given the cold stimulus was removed and the oxygen consumption fell. The 15% oxygen was not only warmer but also humidified. This too may have reduced its value as a cold stimulus.

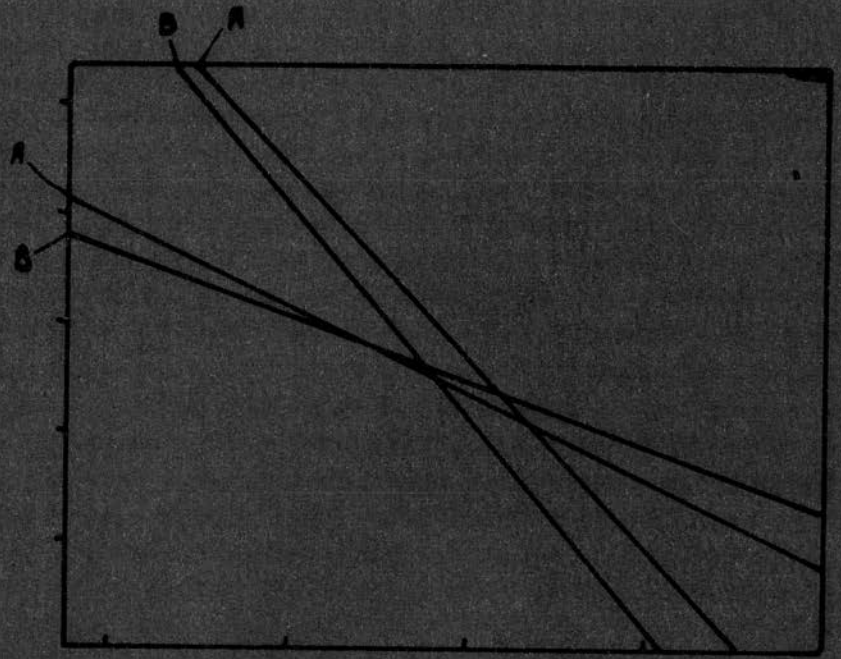
Correlation of gas temperatures with oxygen consumption. So that this explanation can be put on a statistical basis the following hypothesis is suggested:-

1. The temperature of the gases rather than their actual composition affected oxygen consumption.

2. 15% oxygen lowered oxygen consumption because it was warmer and not because it had a lower oxygen content.

On this assumption the presumed temperatures of the air and 15% oxygen have been plotted against values for oxygen consumption taken from Cross et al. (1958) Table 1 period 1 (Series I), Table 2 period 1 (Series II) (both in babies breathing air) and Table 2 period 2 (Series II) (babies breathing 15% oxygen). This graph is shown in Fig. 56.

Two pairs of regression lines can be superimposed on Fig. 56. The first pair summarizes the relation between presumed gas temperature, either air or 15% oxygen, and oxygen consumption (air---15% oxygen Series II). The second pair, taken from Fig. 53, summarizes the relation between presumed gas temperature (temperature of outside air) and oxygen consumption in air in the 2 Series Table 1 Period 1, (Series I) and Table 2 Period 1 (Series II).


B
A
A
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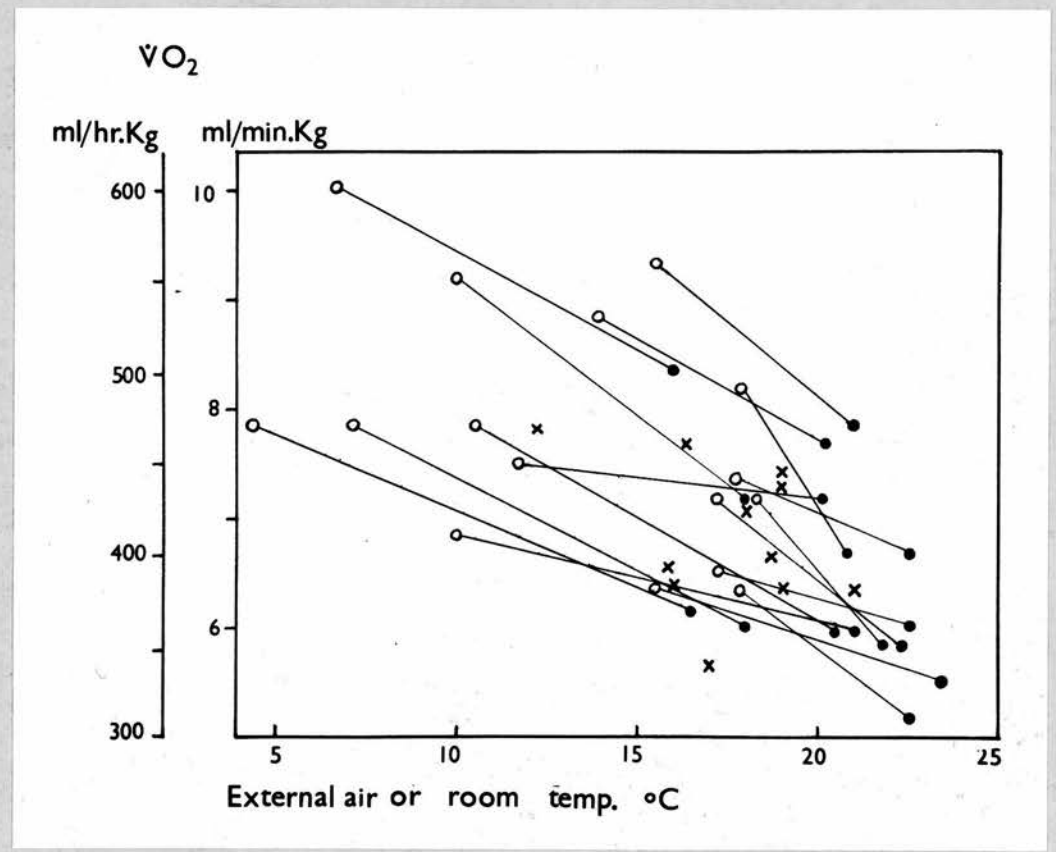
$\dot{V}O_2$
ml/hr.Kg
ml/min.Kg
600
500
400
300
10
8
6
5
10
15
20
25
External air or room temp. °C

Fig. 56

Fig. 56. Oxygen consumption and outside air or room temperature (presumed temperature of inspired air or 15% oxygen). From the data of Cross et al. (1958).

	Symbol	Breathing
Table 1, Period 1 (Series I)	X	air
Table 2, Period 1 (Series II)	O	air
Table 2, Period 2 (Series II)	●	15% oxygen.

The lines between symbols O and ● join measurements of oxygen consumption on the same baby in air and in 15% oxygen.

Transparent flap

The two pairs of regression lines on the flap can be superimposed on the graph.
1st pair indicated by (a) and (a), summarizes the relationship between (1) oxygen consumption in air (symbol O) and in 15% oxygen (symbol ●) and (2) presumed temperature of air or 15% oxygen. (Values from Series II). The correlation coefficient $r = -0.67$ ($P<0.001$)

and $x = -2.82\,y + 36.7$

$y = -0.159x + 9.72$.

2nd pair indicated by (b) and (b) summarizes the relationship between (1) oxygen consumption (a) in air before 15% oxygen (symbol O) (b) in air in the 1st period of Series I (symbol X), (2) Presumed temperature of air breathed.

Correlation coefficient $r = -0.53$ ($0.01>P>0.001$),

and

equations for x on y and y on x, as in Fig. 53.

Correlation coefficient for all 3 sets of values

$r = -0.65$ ($P < 0.001$)

Discussion (cont'd).

It will be seen that the two pairs of regression lines are virtually identical. This finding suggests that gas temperature and oxygen consumption are related in the same way in both. It seems that the higher temperature of the 15% oxygen is sufficient to account for the fall in oxygen consumption and that it is not necessary to invoke any other factor.

It will be seen in Fig. 56 that the values for oxygen consumption in 15% oxygen do not depart from the tendency set by the measurements in air. The lines joining the paired measurements of oxygen consumption in air and 15% oxygen pass through, or close to, the measurements of oxygen consumption recorded in the control period in infants breathing air.

The regression lines from Fig. 53 are approximately parallel to the air——15% oxygen lines. There is a high correlation between the presumed temperature of the gas, whether 15% oxygen or air, and the oxygen consumption, ($r = -0.65$, P less than 0.001).

The plethysmograph temperature was not a factor affecting the change in oxygen consumption when 15% oxygen was given. The switch from air to 15% oxygen was accomplished in about 5 minutes and it seems highly unlikely that the room temperature or the plethysmograph temperature could have changed significantly in this short time.

Although the explanation presented above seems correct it has not yet been confirmed experimentally.

Conclusion. In conclusion it is suggested that it is not necessary to invoke any specific effect of 15% oxygen and that if cooler outdoor air had been followed by room air and not 15% oxygen there would have been a fall in oxygen consumption.

Discussion (cont'd).

It appears likely that the fall in oxygen consumption observed when 15% oxygen was given was due to the higher temperature, and possibly the higher humidity of the 15% oxygen.

The work of Oliver and Karlberg, 1963.

Although the explanation concerning the cooling of the facial skin can be confidently proposed for the difference between the results presented here and those of Cross et al. (1958) the same explanation cannot be advanced for the discrepancy from the results of Oliver and Karlberg (1963). In the latter work the hood temperature, (environmental temperature) was the same whether the infant was breathing air or 15% oxygen and no explanation can at present be advanced for this apparent conflict.

Discussion (cont'd).

PROBABLE EFFECT OF MORE SEVERE HYPOXIA ON INFANTS.

The evidence in animals shows quite clearly that the greater the hypoxia the greater will be the fall in oxygen consumption. This was commented on by Cordier and Mayer (1935), "On observe qu'au-dessous de la tension critique la consummation d'oxygène est d'autant plus faible que la tension d'oxygène dans l'air inspiré est plus basse." The same effect was observed by the authors mentioned in the early part of the discussion (pp. 122-124). It seems very unlikely that the newborn infant will differ from other species in this respect. This suggests that hypoxia more severe than that induced by 15% oxygen, for example 10% or 12% oxygen, will lower oxygen consumption in babies.

The most obvious method for seeking confirmation of this view is to give low oxygen mixtures to infants but this was not considered to be ethical. Cross et al. (1958) also suggested that it might be unethical. 15% oxygen itself is regarded as justifiable and safe and it has been given frequently without any reports of ill effects (Cross and Warner, 1951; Cross and Oppé, 1952; Cross, Hooper and Lord, 1954; Brodie, Cross and Lomer, 1957; Cross et al. 1958; Oliver and Karlberg, 1963).

Sjöstedt and Rooth (1957) considered the low oxygen tensions in foetal blood and suggested that 15% oxygen might be therapeutic in the case of premature infants. In a trial of the effect of 15% oxygen on full term infants this gas was given for as long as one week. No ill effects were noted but the rectal temperature was rather low. Following this trial premature infants were exposed to 15% oxygen for long

Discussion (cont'd).

periods without any ill effects, (Engleson, Rooth and Sjöstedt, 1958). The rectal temperatures were rather low - 33°C in the first few days rising to 36°C at 10 days. This may have been due to the incubator temperature which was about 29°C (about 84°F).

In a careful follow up study (Rooth, Engleson and Törnblom, 1966) infants treated with 15% oxygen were compared with controls of the same birth weight group who had been breathing air otherwise both groups were treated by orthodox methods. They concluded that "Although no final conclusion may be drawn with regard to the value of treatment of premature infants in low oxygen tension, the present results speak in favour of it."

Dangers of breathing low oxygen mixtures.

On the other hand some workers have shown that oxygen in concentrations of less than 15% does have ill effects. Dawes (1965) pointed out that with increasing asphyxia pulmonary vascular resistance will increase, the ductus arteriosus will relax, and the shunt through the ductus may become predominantly right to left. A vicious circle may be created. These changes have been demonstrated in hypoxic newborn infants.

Cardiovascular effects. Eldrige and Hultgren (1955) during a study of the closure of the ductus arteriosus gave 12% oxygen to 4 normal infants. All were thought to show a right to left shunt through the ductus. One infant aged 14½ hours demonstrated a marked fall in oxygen saturation from 92% on air to 57% on 12% oxygen. "This was accompanied by visible generalised cyanosis and somnolence. After room air breathing was resumed, the cyanosis promptly disappeared and no subsequent ill effects were noted." Because of this incident they did not carry out any further studies with 12% oxygen. They drew attention to a similar precipitous fall in oxygen saturation during breathing of low oxygen

Discussion (cont'd).

mixtures demonstrated by Burchell, Swan and Wood (1953) in an older patient with pulmonary hypertension and patent ductus arteriosus.

Adams, Lind and Rauraino (1958) found very variable changes in the systemic and pulmonary artery pressures of 3 normal infants given 10% oxygen.

Saling (1960) performed cardiac catheterization in a series of normal infants aged less than 6 hours and measured the changes in blood oxygen tension. He found that 13% oxygen caused an increase in right to left shunt in every infant. Hypoxia caused deeper and more frequent respirations, with pallor and slight cyanosis.

Moss, Emmanouilides, Adams and Chuang (1964) gave 13% oxygen in nitrogen to 12 normal infants and found that in their hands the risks proved negligible. Hypoxia consistently caused an increase in pulmonary arterial pressure and often the appearance of a left to right shunt. A left to right shunt rather than a right to left was evident because usually the systolic pressure remained greater than the pulmonary arterial pressure although hypoxia lessened the difference. In a few babies ductus that previously were closed reopened during hypoxia.

Although Moss et al. (1964) never found evidence of a left to right shunt the mean pulmonary arterial pressure slightly exceeded the mean aortic pressure in 3 of 15 infants, (Table 2, cases 9, 11 and 15). Had their methods been more sensitive (they measured the change in oxygen saturation) or the hypoxia more severe right to left shunt might have been observed. In 5 of 12 children there was a fall in systemic arterial pressure. They suggested that the effects

Discussion (cont'd).

of crying might be responsible for the responses observed by Eldridge and Hultgren (1955) but this is a hazard one can hardly avoid.

A similar fall in systemic pressure in young infants (mean fall 21%) with hypoxia induced by breathing 10% oxygen was found by James and Rowe (1957). 10% oxygen produced a precipitous fall in oxygen saturation to a mean of 44%. It was noticed that during hypoxia when the arterial oxygen saturation was about 50% the only abnormal finding was of mild somnolence in all infants, but when the saturation fell to 30-40% the infants began to be breathless finally "crying strenuously sometimes in a gasping fashion." "One infant had a period of apnoea at the height of the anoxia." They also found that the colour did not appear to be a good index of the degree of desaturation, pallor more than cyanosis being the rule, (cf. Results page 120). In 5 infants they concluded that there was a right to left shunt through the ductus produced by the rise in pulmonary arterial pressure and the fall in systemic pressure.

Berg and Celander (1965) found that 10% oxygen may cause severe cardiac disturbances and a sudden reduction in pulse rate to half the initial figure. "This change occurred abruptly and could be explained by a nodal block." "The performance of the heart can be disturbed by quite a moderate degree of hypoxia."

Respiratory effects. Miller and Behrle (1954) found that 10% and 12% oxygen depressed respiration in infants aged less than 10 days. "So many of the infants in the oldest group receiving 12% oxygen cried and struggled after 5 or 6 minutes of hypoxia, that satisfactory records could not be obtained." "The test period was

limited to 5 minutes when 10% oxygen was given because it was found, in using 12% oxygen, that several infants of the oldest group cried and struggled at about this time and a few of the youngest group seemed to be considerably depressed after 8 minutes of breathing 12% oxygen. In all infants there was visible cyanosis after four or five minutes of breathing either mixture." One test on a newborn infant had to be interrupted because of the infant's depressed state.

Miller and Smull (1955) found that none of the group of older premature infants would stay more than 2 minutes in 12% oxygen without struggling.

Howard and Bauer (1949 and 1950) also found that 12% oxygen depressed the minute volume in normal infants and that in 12-14% oxygen the rhythm frequently changed to a Cheyne Stokes pattern. "We felt that the infant with this type" (of respiration) " was always under a strain and that it wasan indication of impending harm." Other aspects. For the sake of completeness one may include the results of Stern, Leduc and Lind (1964) who gave 10% oxygen for 5 minutes to 10 normal infants. No ill effects were reported, and there was no change in the excretion of catechol amines.

Finally the effect of hypoxia on some newborn animals must be considered. Cross, Dawes and Mott (1959) found that in 6 lambs, out of a total of about 30, aged 4 to 13 hours, breathing abruptly stopped when the percentage of oxygen inspired was reduced to values between 9.4% and 15.1%. 5 needed artificial respiration, prolonged in 1, before breathing was restored. When 15% oxygen was given to newborn rats in a warm environment it caused increased activity and cyanosis and on 10% oxygen some rats developed slow gasping respiration and became ashen coloured (Taylor, 1960).

Discussion (cont'd).

Conclusion. Because of these dangers and for ethical reasons it was not thought desirable to pursue the present work to its logical conclusion and to induce hypoxia more severe than that caused by 15% oxygen.

Oxygen Consumption in Hypoxia caused by Disease.

Severe hypoxia occurs in newborn infants who have cardiovascular or pulmonary disease and studies of oxygen consumption in such conditions are of considerable interest, although in many cases the hypoxia may be accompanied by changes in acid base balance. The most obvious examples of naturally occurring hypoxia in the newborn are cyanotic congenital heart disease, respiratory distress syndrome and birth asphyxia.

Congenital heart disease.

Brück, Adams and Brück (1962) examined the oxygen consumption of infants with cyanotic congenital heart disease and chronic hypoxaemia in response to a standardised cold stress previously used in a large number of normal infants (Brück,1961). Babies who had moderately severe hypoxia (oxygen contents of greater than 10 vols. %), but without heart failure had a normal oxygen consumption in the cold. The youngest of these subjects aged 10 days had an oxygen content of 12.3 vols.%, and an oxygen saturation of 59% which corresponds to an arterial oxygen tension of 23 mm. Hg. at pH 7.4, and slightly more at a lower pH (Hellegers, 1961). This is considerably less than that expected in the normal infant breathing 15% oxygen (47-50 mm. Hg., according to Graham, 1954), but the oxygen consumption in the cool was normal.

On the other hand three infants with more severe chronic hypoxaemia, oxygen content of 6 vols. % or less,

Discussion (cont'd).

had an abnormally small metabolic response to the standard cold stress. Two of these babies had oxygen contents of 3.9 and 5.4 vols. O_2 %, and arterial oxygen saturations of 31% and 35%, which correspond to pO_2 of about 14 and 16 mm. Hg. again assuming pH 7.4 (Hellegers, 1961). Their ages were 3 weeks and 7 months. The third infant had hypoxaemia and a meningo myelocele without cardiac abnormality but Cross and Hey (unpublished data) showed that the metabolic response to cold was reduced in this condition in one baby who did not appear to have hypoxaemia.

Levison and Swyer (1965) pointed out that disturbance of acid base balance may contribute to the effect of hypoxia on oxygen consumption. They studied two babies both with cyanotic congenital heart disease and both with arterial oxygen tensions of 20 mm. Hg. In the first who died at 36 hours oxygen consumption in the warm at an age of 30 hours was reduced to 2.36 mls. min. Kg., (normal according to these authors 5.3 mls/min per Kg.). Despite much intravenous bicarbonate the arterial pH never rose above 7.0 mls. min. Kg. In the second infant, who survived, oxygen consumption at 2 weeks was normal at 6.6 mls. min. Kg. and the pH was normal at 7.36. Similar conclusions were reached by Levison, Delivoria-Papadopoulos and Swyer (1965).

Asphyxia neonatorum.

Babies recovering from asphyxia neonatorum were shown by Burnard and Cross (1958) to have significantly lower rectal temperatures than babies who did not suffer birth asphyxia; this was interpreted as due to depression of oxygen consumption and heat production caused by the asphyxia.

Discussion (cont'd).

Respiratory distress syndrome.

Oxygen consumption has been measured in a baby with severe respiratory distress syndrome by Cross, Hill and Rahimtulla (unpublished - quoted by Cairdner, 1965). When the concentration of oxygen in the inspired gas was reduced below about 60% the baby became cyanosed and there was a fall in oxygen consumption, but when the inspired oxygen concentration was increased, oxygen consumption was restored to its former value.

Ahmed and Scopes (1966) (quoted by Scopes, 1966) studied the metabolic response to cold of infants with the respiratory distress syndrome and made simultaneous measurements of the arterial pO_2. The metabolic response to cold was impaired at a pO_2 of 45-55 mm. Hg. and abolished at a pO_2 of 30 mm. Hg. The pO_2 values were stated to be equivalent to those produced when normal infants breathed approximately 12% O_2 or 8% O_2.

The oxygen consumption of two groups of premature infants of comparable birth weight with and without respiratory distress syndrome was studied by Miller, Behrle, Nieman, Driver and Dudding (1962). In these experiments the ambient temperature was 88-90°F (about 31.5°C) and the relative humidity varied between 20 and 90%. These thermal conditions were considered to be within the neutral temperature range. The mean oxygen consumption of the distressed babies was 5.32 mls. min. Kg. while breathing air which was statistically significantly lower than 7.45 mls. min. Kg. the mean oxygen consumption of the non distressed group. Both groups of infants were aged less than 60 hours and the mean weight of the distressed group was about 1600 grams and that of the healthy group slightly higher at 2000 grams.

Discussion (cont'd).

These values have been given in some detail because it appears that they were not in the neutral range as the authors state but in the cool which is important in the present context. This is well shown by comparison with Table 21 of basal metabolic rates in premature infants from the data of Adams, Fugjwara, Spears and Hodgman (1964). It will be seen that even in the oldest age group quoted by Adams et al. (1964) the oxygen consumption does not approach the values reported by Miller et al. (1962). Also the ambient temperature was lower than that used by Adams et al. although this is not so readily comparable in different apparatus. Levison, Delivoria Papadopoulos and Swyer (1964) found that oxygen consumption was lowered in babies who had severe metabolic acidosis and respiratory distress.

Indirect evidence that oxygen consumption is lowered in respiratory distress syndrome is available from measurements of rectal temperature. Clearly the incubator temperature has a pronounced effect on body temperature but although warm incubators might be expected to raise rectal temperature unduly high the presence of a lowered rectal temperature might be of more significance. According to Avery (1962) persistent hypothermia is seen in the sicker infants. Troelestra, Jonxis, Visser and vander Vlugt (1964) made a similar observation.

However it is well established that there is a metabolic acidosis in respiratory distress syndrome (Usher, 1961), and in view of the recent finding of Levison and Swyer (1965), this must be taken into account in evaluating the causes of depression of oxygen consumption in respiratory syndrome.

TABLE 21

MINIMAL OXYGEN CONSUMPTION IN PREMATURE INFANTS AT ENVIRONMENTAL TEMPERATURES OF 32-34°C. R.H. 40-60%.

Adams et al., 1964*

	AGE hours	WEIGHT G.	OXYGEN CONSUMPTION MLS/MIN.KG. (S.T.P.D.)
Mean	9.8 (2½-24 hrs)	1,693	4.5
1 S.D.	7.5	339	0.9
Mean	54.9 (25-76 hrs)	1,704	6.4
1 S.D.	16.5	328	1.2
Mean	10.7 (6-18 days)	1,702	6.5
1 S.D.	3.6	344	0.8

* Adams, Fugjwara, Spears and Hodgman, 1964.

Discussion (cont'd).

Lastly studies comparing the oxygen consumption of infants born at high altitudes and breathing atmospheric air of low oxygen content with that when breathing simulated sea level air would be interesting and ethically justifiable but, not surprisingly, do not appear to have been done.

Conclusion.

The work performed by the author has shown that oxygen consumption in normal newborn babies does not appear to be lowered by 15% oxygen, and an explanation of the discrepancy between this and an earlier report has been advanced. It has been pointed out that in the well established animal work which showed that hypoxia did lower oxygen consumption the concentrations of oxygen used were always less than 15% oxygen. Evidence has been presented to show that in some pathological conditions in babies severe hypoxia is associated with and probably causes a lowered oxygen consumption. It is suggested that in babies in the cool, oxygen concentrations lower than 15%, perhaps of the order of 10-12%, would lower oxygen consumption but the reported incidence of side effects was thought to be too great for such experiments to be justifiable. There would seem to be little purpose or validity in exposing any baby to serious risk to seek evidence of a probability which has been amply confirmed in animal work when there is already supportive clinical evidence.

APPENDIX 1

The use of the modified scale to measure the volume changes of the differentiating float.

The excursions of the differentiating float were measured by reading the lengths off against a simplified scale which was a modification of the true calibration. The method was devised by Dr. Hill, and eased and accelerated the work of measuring up the oxygen consumption record because it avoided the necessity to estimate fractions of an interval (see Fig. 57).

If a series of lengths is measured on the modified scale the total obtained is 0.5 ml per measurement greater than on the true scale. If $\frac{n}{2}$ is subtracted from the total obtained on the modified scale, where n is the number of values, the result does not differ from the total obtained on the true scale by more than 0.5 ml. Usually a series of 20 values was measured and a value of 10 was subtracted from the total obtained from the modified scale.

The use of the correction factor is illustrated in the 3 worked examples below where the groups of lengths, which in Figure 57 are designated by letters A, B and C have been measured on both the true and the modified scales.

	TRUE SCALE	MODIFIED SCALE
Group A	1 2 3 4 5	2 2 4 4 6
	= 15	= 18
		Correction factor 2.5
		18 - 2.5 = 15.5

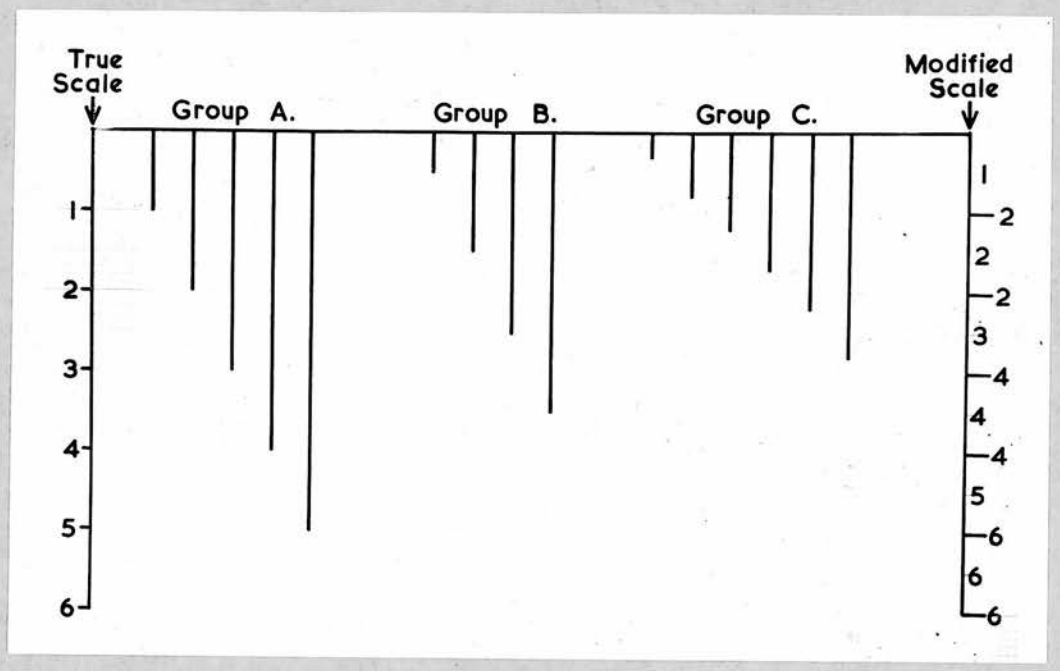

Fig. 57. The true and modified scales used to measure the excursions of the differentiating float.

APPENDIX 1 (cont'd).

	TRUE SCALE	MODIFIED SCALE
Group B	0.5 1.5 2.5 3.5 = 8	1 2 3 4 = 10 Correction factor 2 10 - 2 = 8
Group C	0.3 0.8 1.2 1.7 2.2 2.8 = 9	1 1 2 2 3 3 = 12 Correction factor 3 12 - 3 = 9

APPENDIX 2

Paired measurements of oxygen consumption in babies in a warm environment were made when there was no change in the inspired gas. The mean difference between such pairs (0.8%) was not significantly different from zero and the standard deviation of the differences was 10%. Cross et al. (1958) found a mean fall in oxygen consumption of 17% after air was changed to 15% oxygen. We wish to show that sufficient experiments have been performed using the present experimental method to rule out such a possible result under the present conditions.

The minimum necessary number of paired experiments assuming the same standard deviation of the difference (10%) may be calculated from the Student's t test formula for the significance of the difference of a mean from some assigned known value (null hypothesis). Here the null hypothesis is no change (X) and the postulated mean change under test ($\bar{x}$) is -17. Substituting in:

$$t_{(\text{for } (n-1))} = \left[(X - \bar{x})\sqrt{n-1}\right] \div \sigma$$

taking $t = 4$

$$4 = \pm 17\sqrt{n-1} \div 10$$

$$4 = 1.7\sqrt{n-1}$$

$$n = 5.53 + 1$$

As a second approximation reading t for n = 6 (when p = 0.01)

$$3.71 = 1.7\sqrt{n-1}$$

$$n = 4.76 + 1$$

Thus the probability is a little less than 1% that 6 experiments would not have been enough to rule out a change of 17%. By a similar procedure we may calculate that 10 experiments would certainly suffice to rule out more than a 1:1000 chance of a true mean change of 17%.

APPENDIX 3

Calculation of gas velocity in the work of Cross et al. 1957 and 1958

It will be seen that this calculation can only be very approximate. The face mask used in the work above was made from a 3 cm. diameter perspex tube, split longitudinally, and curved to fit the infant's face and nose. The exact shape into which the perspex was moulded is not known but from Fig. 1 in Cross et al. (1957) it can be seen that it was approximately parallel to the infant's nose, and that the parts in contact with the infant's cheek formed about 25% of the whole length.

Area beneath the mask. (Fig. 58).

Assuming that the perspex mask, seen in cross section, formed a right angled isosceles triangle,

Perimeter of triangle - base = 9.4 cm. - $\frac{1}{4}$ (9.4 cm.)

$\simeq$ 7 cm.

where 9.4 = 2 x 3.142 x $\frac{3}{2}$

(diameter of tube = 3 cm)

where 3.142 = Pi (π)

and $\frac{1}{4}$ (9.4) = part of tube in contact with cheek

$\therefore$ The area beneath the mask $\simeq$ 6.1 sq. cm.

Cross sectional area of end of infants nose

The noses of 9 normal infants were measured, (mean weight 3.50 Kg.). The mean breadth between the outer skin of the nostrils was approximately 2.2 cm. The mean distance from the tip of the nose to the junction of the nose with the upper lip was approximately 1.1 cm.

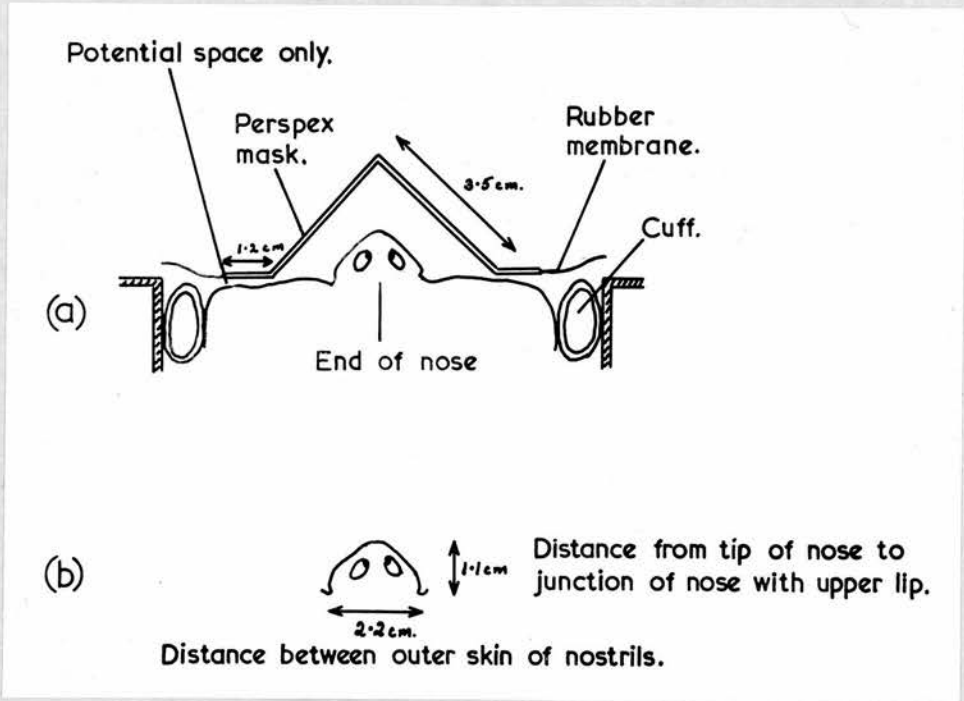

Fig. 58. Calculation of gas speed in the experiments of Cross et al. (1958)

The upper diagram (a) indicates the arrangement of the perspex face mask, here drawn as being right angled at the apex, and the infant's nose. The lower diagram (b) indicates the mean measurements of the noses of 9 normal full term infants.

Diagram (a) is based on Fig.1(b) of Cross, Tizard and Trythall (1957).

APPENDIX 3 (cont'd).

Assuming that the end of the nose seen in cross section forms a right angled isosceles triangle,

Cross sectional area of end of nose = 1.2 sq.cm.
Area between mask and nose = 4.9 sq.cm.

The mean rate of gas flow in Table 1 Period 1 of Cross et al. (1958) was 1851 mls/min (obtained from original experimental protocols).

$$\text{Gas speed} = \frac{\text{flow rate}}{\text{area}}$$

$$= \frac{1851}{4.9}$$

$$= 6 \text{ cm/sec.}$$

It must be emphasized that nothing more is claimed for this calculation than that it gives a rough idea of the gas speed, and that this was not obtainable in any other way.

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